Aims & Scope

The European Respiratory Journal (ERJ), the official Journal of the European Respiratory Society, publishes, in the English language, clinical and experimental work dealing with all aspects of respiratory medicine. In addition to original material, the ERJ prints Editorials and Reviews, as well as Technical notes, Letters and Correspondence. This Journal is abstracted/indexed in: Ad Referendum, ADONIS, Biological Abstracts/BIOSIS, Chemical Abstracts, Current Contents: Life Sciences, Current Contents: Clinical Medicine, Elsevier BIOBASE/Current Awareness in Biological Sciences, EMBASE/Excerpta Medica, Index Medicus/MEDLINE, Medical Documentation Service, Research Alert, Science Citation Index, SciSearch, SIIC Data Base and CABI Global Health.

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every breath counts

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41. The COPD patient experience: care and management

164 Lung cancer and COPD multidisciplinary teams: Exploring comparisons of patient perceptions
Christine Blunt1, Joan Curriz1, Tony Leiba, Sarah Elkin2. 1Facility of Health and Social Care, London South Bank University, London, United Kingdom; 2Respiratory Medicine, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Background/Objectives: Multidisciplinary teams (MDT’s) and effective team working are considered key to providing quality, patient centred care. However there is a paucity of research regarding patient perceptions of these teams including for chest disease. The qualitative study aimed to explore the differing patient perceptions of effectiveness in two disease specific teams.

Methods: 12 patients (lung cancer n=6, Chronic Obstructive Pulmonary Disease n=6) 64-84 years in contact with their respective multidisciplinary teams for 3 months or more were interviewed using a semi-structured format. Data from interviews was analysed based on Interpretative Phenomenological Analysis.

Results: Several themes were identified, commonalities between teams were: 1) Doctors seen as core team members whilst other health professional consultations perceived as inferior. 2) GP's not considered part of a team. 3) Team effectiveness and morale often judged by attitude of frontline administrative staff. Differences: lung cancer patients perceived 1) Efficacy of service upon outpatient clinic waiting times. 2) A greater need for privacy during consultations and when leaving. 3) Greater awareness of MDT communication and meetings. 4) Greater awareness of nurse specialists. COPD participants 1) Accessibility and quicker response to request to be seen by health professional.

Conclusions: These patient groups suggest a traditionalist view of physicians providing treatment. Increasing information regarding health professional specialties, team communications and attention to psychosocial issues may increase patient satisfaction and confidence in MDTs.

165 Developing a framework for palliative interventions in respiratory services in Ireland: One year into an action research project
Bettina Keen1, Patricia White1, Rory O'Donnell1, Caitriona Corcoran1, Kay Kehaly1, Marie Lynch1, Liam O’Sorain2. 1Department of Respiratory Medicine, St. James’s Hospital, Dublin, Ireland; 2Palliative Care Services, St. James’s Hospital, Dublin, Ireland

Background: Traditionally, palliative care services have centred on the needs of patients with malignant disease and there is little evidence of the integration of palliative care into disease specific services in Ireland. The purpose of this research was to devise, implement and evaluate palliative care responses for people with advanced respiratory disease.

Methods: An action research methodology has been adopted for this multi-site research. This approach provides the opportunity for collaboration, reflection and exploring ways of improving service delivery. It incorporates both qualitative and quantitative methodologies and includes an expert focus group, survey of palliative care education needs, interviews with patients and families and retrospective chart reviews.

Results: To date, the initial planning and action cycles have started. The project outcomes and potential barriers have been identified through an expert focus group.

Ongoing retrospective chart reviews highlight the low level of referrals to specialist palliative care. Results from the quantitative survey showed a lack of understanding of what palliative care entails, with 93% of respiratory staff interested in attending palliative care education. Further actions include the establishment of multi-disciplinary, multi-site team meetings to improve patient care.

Conclusions: The reactive and reflective nature of action research has been advantageous in bringing about change in a demanding health care system. This project is developing and evaluating a palliative care model of support, intervention and referral pathways for people with advanced respiratory disease.

166 COPD patients coping with breathlessness during daily living – A multi-modal grounded theory
Lene Bastrup Jørgensen1, Ronald Dahl2, Preben Ulrich Pedersen3, Kirsten Elisabeth Lomborg1. 1Department of Nursing Science, School of Public Health, Aarhus University, Aarhus, Denmark; 2The Department of Pulmonary Medicine, Aarhus University Hospital, Aarhus, Denmark

Introduction: Grasping the complexity of COPD patients coping with breathlessness during daily living has not yet been achieved.

Purpose: To develop a grounded theory of COPD patients’ coping styles by investigating possible interrelations between the physiological, cognitive, affective and psychosocial dimensions in coping.

Materials and methods: Twelve patients with moderate to severe COPD were included during hospitalization for an acute exacerbation of COPD. We chose a multi-modal grounded theory design with concurrent data collection and analysis, and a constant comparative analytic process of interpretation of the data material as a whole. Data were collected both at hospital and in the patients’ home after discharge. Data were derived from video, interview, medical history, demographics, scores on a modified Borg Scale and recordings of SaO2, heart rate, energy expenditure and level of MTE. The data material comprised 24 interviews, 50 recordings of videos, 50 video transcriptions, 50 sets of measurements of physiological parameters, 50 set of scores on the modified Borg Scale and 12 sets of demographic information.

Results: The main concern for the participants appeared to be an endless striving for economizing on intra-, extra-, and interpersonal resources with the main purpose of preserving their existence with breathlessness. Suggesting a coping trajectory, four coping styles emerged in this self-protective process corresponding with the degree of pulmonary function, level of physical activity, energy expenditure and social status.

Conclusion: COPD patients’ coping styles appear to correspond with their physical and psychosocial condition suggesting a “COPD coping trajectory”.

167 Living with severe chronic obstructive pulmonary disease (COPD): The male carer’s story
Terry Robinson, Giles Fitch. Respiratory Nurses, Harrogate and District NHS Foundation Trust, Harrogate, North Yorkshire, United Kingdom

Introduction and objectives: The aim of this qualitative study was to gain a better knowledge and understanding of the male caring role in COPD, and to explore the ways in which individual carers live with COPD patients.

Methods: A prospective unstructured audiotaped interview using a phenomenological approach was used to collect data from ten men (mean age 70.1 years) living with wives or partners who had severe COPD.

Results: Recurrent themes emerged. Most participants reported lack of support at a social isolation as they lacked the network of friends and family around them that women appear to have. Previously enjoyed activities such as holidays and sexual relationships were no longer possible for many, leading to increased stress and resentment. Hospital admissions led to increased work load and even less time for the men, and many described how the future filled them with fear, especially if their partner deteriorated further, or if their own health deteriorated. Surprisingly six men did not perceive themselves as carers, preferring the word “partner” to carer. As they did not implement themselves as carers they did not ask for help or to be asked for help. Five men felt that caring did not come naturally to men, and felt women were better suited to the role as they had historically raised children and run the family home.

Conclusion: Severe COPD impacts on all aspects of male carers’ lives. The specific needs of male carers should be considered when designing and delivering services to this patient group.

168 The experience of not being able to stop smoking despite having COPD
Brit-Marie Ekland1,2, Siv Nilsson2, Linea Hedman1, Inger Lindberg2. 1The OLIN-Studies, Norrbonen County Council, Lulea, Sweden; 2Health Sciences, Division of Nursing, Lulea University of Technology, Lulea, Sweden

Background: COPD (Chronic Obstructive Pulmonary Disease) is one of the most widespread lung diseases and a growing cause of suffering and mortality worldwide. It is predicted to become the third leading cause of death in the near future. Smoking is the most important risk factor and 50% of smokers develop COPD. Smoking cessation is the most important intervention to improve prognosis for individuals with COPD.

Aim: To describe the experience of not being able to stop smoking among persons diagnosed with moderate COPD.

Methods: Ten smokers (5 women) with COPD, GOLD stage II, participated in semi-structured interviews. The data was analysed using qualitative content analysis. The participants were recruited from the OLIN studies in Northern Sweden.

Results: The analysis resulted in two themes: 1) Life is governed by a long smoking history that is difficult to break and 2) To be aware of and enlightened, but lacking ability to make a decision, and in five categories: That it is the wrong time in life to stop; To break a lifelong pattern is impossible; That planning to stop does not lead to results; Being aware of the consequences of continued smoking and to have received help and support but not wanting to be patronized. Although they knew about the harmful effects of smoking, difficulties in everyday life aggravated smoking cessation. To have plans to stop smoking is not enough, it is also necessary to get motivation and support from the social environment at the right time.

Conclusion: The individual life situations are very important for successful smoking cessation. Health professionals should be even more sensitive and provide an individually tailored support when an individual decides to stop smoking.
42. New insights in the treatment of idiopathic pulmonary fibrosis

The Integration of Respiratory Services... Is it the way forward?
Alison Graham, Jacqueline Bayliss, Kath Morgan. Integrated Respiratory Service, Cheshire East Community Health, Macclesfield, Central and East Cheshire, United Kingdom

Aim: To assess the impact of the introduction of an Integrated Respiratory Service in Central and East Cheshire by looking at admission avoidance, reduction in admissions, length of patient stay and oxygen prescribing costs.

Introduction: The Integrated Respiratory team (IRT) is an in-reach and out reach specialist respiratory service for patients with COPD and other lung diseases in Central and East Cheshire. The IRT offers a 7 day service which incorporates acute hospital care, same day & early discharge services for patients with COPD, patient assessment and support within their place of residence to facilitate hospital admission avoidance, community & hospital based specialist nurse led clinics, a oxygen assessment service, pulmonary rehabilitation, respiratory education and palliative care.

Methods: An analysis of service activity data was undertaken for the period 1st April, 2010 to 31st January, 2011.

Key Achievements: The IRT has managed 2778 referrals, reduced the oxygen prescribing budget by £120,000, avoided the admission of 225 patients, supported the early discharge of 446 patients and reduced the average length of stay from 6 to 3 days. The IRT has managed 1366 new and follow up patients in the specialist community clinics. This equates with a potential predicted annual cost-saving of £163,079.63 in the oxygen prescribing budget, suggests a annual cost-saving of between £453,269 and £634,577 as a result of the reduction in length of stay and in addition an annual saving of approximately £481,162 for those patients on the early and supported discharge programme.

Conclusion: The Integration and collaboration of Respiratory Specialist Services is not only providing the best care, it is cost effective.

Table 1. Country-level concerns for the future, earning ability, and social factors

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<td>Unable to maintain lifestyle</td>
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<td>Cough embarrassed in public</td>
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Conclusions: Respondents felt they were restricted by their COPD in terms of achieving life goals, socialising with others and providing usual family care. The aim of this study was to ascertain the social and financial impact of COPD on this age group. The country level data are presented from a multi-country cross-sectional survey.

172 Efficacy of BIBF 1120 in patients with IPF is dose-dependent: Results from the TOMORROW trial
Ulrich Costabel, Luca Richeldi, Moses Selman, Dong Soon Kim, Kevin Brown, Kevin R. Flaherty, Paul W. Noble, Ganesh Raghu, Michèle Brun, Abhya Gupta, Matthias Kuehle, Nolwenn Juhel, Roland Moena Bois, R. Ruhland, Limkod and Medical University, University of Duisburg-Essen, Essen, Germany; 2Center for Rare Lung Disease, University of Modena and Reggio Emilia, Modena, Italy; 3Instituto Nacional de Enfermedades Respiratorias, “Ismael Costi Villegas”, Mexico, Mexico; 4Division of Pulmonary Medicine, Critical Care Medicine, Asian Medical Center, Seoul, Korea; 5Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, National Jewish Health, Denver, United States; 6Division of Pulmonary Medicine, Pulmonary and Critical Care Division, University of Michigan, Ann Arbor, United States; 7Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Duke University Medical Center, Durham, United States; 8Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, United States; 9Boehringer Ingelheim Pharma G.m.b.H. & Co. KG, Boehringer Ingelheim, Biberach, Germany; 10National Heart & Lung Institute, Imperial College, London, United Kingdom

Background: BIBF 1120 is an inhibitor of tyrosine kinase receptors involved in lung fibrosis progression.

Methods: The TOMORROW trial was a 12-month, placebo (PBO)-controlled study to investigate efficacy and safety of BIBF 1120 (50 mg, 100 mg, 200 mg, 300 mg per day) in IPF (8–5 pts per group). Annual rate of decline in forced vital capacity (FVC) was measured.

Results: FVC decline decreased from 0.17 L/year (50 mg) to -0.06 L/year (300 mg) vs 0.19 L/year in PBO (300 mg vs PBO: p=0.014; closed-testing multiplicity-corrected: p=0.0064). Absolute changes from baseline in % pred FVC were -6.00, -4.58, -4.90, -3.15 and -1.04% in PBO and rising dose groups (200 mg: p=0.031; 300 mg: p=0.0002).

Conclusions: Respondents felt they were restricted by their COPD in terms of achieving life goals, socialising with others and providing usual family care. The results confirm the high social impact of COPD and financial concerns are of particular importance for working age patients.

The individual social and financial burden of COPD
Monica Fletcher, Helen Allbrown, Christine Mercier, Samantha Walker.
Research, Education for Health, Warwick, United Kingdom; 2Department of Respiratory Medicine, Concord Hospital, Concord, New South Wales, Australia

Introduction: An increasing number of people with COPD are under 65 years. The aim of this study was to ascertain the social and financial impact of COPD on this age group. The country level data are presented from a multi-country cross-sectional survey.

Method: 2426 respondents from Brazil, China, Germany, Turkey, UK and US were recruited utilising a mixed methods design. Data was collected on the financial impact of COPD on individuals and their families, including effect on household income and expenditure, willingness to pay, for future, and social impact.

Results: 49% (1180) males, m 56.4yrs, and 29% employed. Respondents felt unable to plan for the future or maintain lifestyles. Over 1/3 felt household income had decreased. 17% a burden to friends and family, and 26% unable to care for children/family as before. Over 50% went out less, and similar numbers felt embarrassed by their cough. Over half felt their condition had stopped them achieving life goals or dreams.

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Conclusions: Respondents felt they were restricted by their COPD in terms of achieving life goals, socialising with others and providing usual family care. The results confirm the high social impact of COPD and financial concerns are of particular importance for working age patients.

The Integration of Respiratory Services... Is it the way forward?
Effect of baseline FVC on preservation of lung function with BIBF 1120: Results from the RECAP extension study

Lucia Richel1, Ulrich Costabel1, Moises Selman1, Dong Soon Kim4, Kevin R. Flaherty2, Paul W. Noble6, Ganesh Raghu1, Arata Azuma4, Michele Brun4, Abiya Gupta5, Matthias Kluglich5, Nozhenn Juhe1, Roland M. du Bois1
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Background: BIBF 1120 is an inhibitor of tyrosine kinase receptors involved in the progression of lung fibrosis.

Methods: The efficacy and safety of 50 mg, 100 mg, 200 mg and 300 mg daily doses of BIBF 1120 were evaluated in 428 patients diagnosed with IPF in a Phase 2 randomized, double-blind placebo (PBO)-controlled trial. Subgroup analyses of the annual rate of decline in forced vital capacity (FVC) by baseline lung function were carried out to evaluate the impact of stage of disease on the effect of BIBF 1120.

Results: Baseline FVC was similar in all groups (mean: 2.8 L; 81.3% predicted). The annual rate of decline in FVC was -0.060 L/year with BIBF 1120 300 mg vs -0.186 L/year with PBO [n=22; p=0.794]. Patients with baseline FVC ≥70% of predicted value showed almost no FVC decline with BIBF 1120 300 mg [-0.010 L/year vs -0.160 L/year; p=0.112] and ≥90% of predicted value [-0.019 L/year vs -0.186 L/year; p=0.088] of predicted value; however, these findings were based on small sample sizes and the differences did not reach significance.

Conclusions: The effects of IPF treatment may be more easily demonstrable in patients with FVC values closer to predicted values.

The long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF): Interim data from the RECAP extension study

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Introduction: The CAP (CAPACITY) trials were randomized controlled studies evaluating pirfenidone (PFD) in patients with IPF. Pooled data from these studies support a treatment effect on forced vital capacity, progression-free survival, and 6-minute walk distance. To examine the long-term safety of PFD, an open-label extension study for eligible CAP patients was initiated (RECAP). An interim analysis of safety data from RECAP is presented.

Aims and objectives: Examine the long-term safety of PFD in patients with IPF.

Methods: Safety data from the RECAP study through Wk 72 were analyzed and compared to pooled safety data from the CAP trials.

Results: In the CAP studies, 779 patients were randomized to treatment with PFD or placebo for ~7.2 weeks. Of these, 603 enrolled in RECAP. At Wk 72 in RECAP, mean exposure to PFD 240 mg/d across both studies was 2.9 yrs (range, 1–4). 114 patients had received PFD 240 mg/d for ≥3 yrs. In RECAP, 98.2% of patients reported ≤1 treatment-emergent adverse event (TEAE) compared to 98.6% in CAP. 12% of patients had a serious TEAE compared to 32.8% during CAP. Common AEs in RECAP were similar to those observed in CAP and were generally mild to moderate in severity. The overall incidence of photosensitivity or rash was lower in RECAP than CAP (19.7% vs. 44.4%); however, patients who received placebo during CAP had a higher incidence than those who received PFD (28.1% vs. 12.3%).

Conclusions: Long-term safety data demonstrate that PFD is safe and generally well tolerated in patients with IPF. Given the unmet medical need and efficacy seen in 3 Phase III studies, PFD has a clear role in the treatment of IPF.

Antifibrotic effects of sulforaphane in human lung fibroblasts from idiopathic pulmonary fibrosis

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Rationale: Nrf2 pathway has been implicated in myofibroblast differentiation, a key step in idiopathic pulmonary fibrosis (IPF) pathophysiology. Sulforaphane (SFN), an isothiocyanate mainly found in cruciferous vegetables, has been shown to activate Nrf2. The aim of this study was to assess the effects of SFN on oxidative stress and fibroblast phenotype in IPF.

Methods: The effects of SFN were assessed on human pulmonary fibroblasts from IPF and control patients in vitro. Oxidant/antioxidant balance, nuclear Nrf2 expression, fibroblast phenotype, in basal and profibrogenic conditions (TGF-β or PDGF-BB stimulation) were experienced.

Results: SFN increased antioxi- dant enzymes and Nrf2 nuclear expression, and decreased oxidative stress in IPF fibroblasts, in basal conditions and after TGF-β stimulation. SFN stimulation induced a myofibroblastic dedifferentiation of IPF fibroblasts with morphologic aspect of control-like fibroblasts and reduction of α-SMA and collagen I expression, proliferation, migration and con- traction. Moreover, addition of SFN after TGF-β and PDGF-BB stimulation, inhibited their deleterious effects on IPF and control fibroblasts, and restored antioxidan t defenses. Nrf2 sRNA transfection abolished antifibrotic effects of SFN.

Discussion: The effects of SFN on cell differentiation have been reported in renal tubular epithelial cells in a rat model of renal fibrosis, but effects on human pulmonary fibroblasts from IPF and control patients were unknown.

Conclusion: These results suggest the potential therapeutic effect of SFN on pulmonary fibroblasts in vitro.

Presence of right ventricular dysfunction predicts dyspnea and quality of life improvements with sildenafil in IPF

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Background: IPF is a progressive lung disease with impaired gas exchange. The STEP-IPF trial was conducted to determine if sildenafil would increase 6-minute walk distance by ≥ 20%. The primary endpoint was not reached, but a sub- analysis tested whether baseline evidence of pulmonary hypertension would predict treatment response.

Methods: Echocardiograms were available for review in 119/180 subjects and read by two cardiologists. Right ventricular hypertrophy (RVT), RV systolic dysfunction (RVD) and RV systolic pressure (RVP) were assessed. A general linear model determined the relationship between cardiac abnormality, sildenafil treatment and improvement in quality of life (QOL) as measured by EuroQol EQ-5D, EuroQol thermometer and SGRQ at 12 weeks.

Results: Mean FVC% predicted was 57%; DLCO% predicted 26%. Prevalence of RVH was 13%; RV systolic dysfunction 19%. Mean RVPV=42.5, measurable in 7/119 subjects. Mean E/e′ measured by STE E′ was 8.2, measured in 68/114 subjects. Mean EuroQol EQ-5D 0.73, and SGRQ 53.1. Significant interactions between RV systolic dysfunction and sildenafil treatment were seen for SGRQ (p=0.048), SGRQ symptom score (p=0.002) and EuroQol Thermometer (p=0.05). Sildenafil treated subjects with RVD improved by 13.4 SGRQ points, 28.0 SGRQ symptom score points, and 17.9 EuroQol Thermometer points vs placebo. Those with RVD treated with placebo increased their SGRQ by 2.9 points, SGRQ symptom score by 3.8 points, and dropped their EuroQol Thermometer score by 1.4 points vs placebo.

Conclusions: In IPF patients with RV systolic dysfunction, sildenafil treatment is associated with improvements in QOL as measured by SGRQ total and symptom scores and EuroQol Thermometer score.

A prospective, non-randomized clinical trial to study the safety and efficacy of the endobronchial autologous infusion of adipose-derived mesenchymal stem cells (ADMSCs) in patients with idiopathic pulmonary fibrosis (IPF)

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Background: IPF is a chronic, progressive, lethal fibrotic lung disease of unknown etiology and treatment yet unfortunate. The aim of the study was to investigate the safety and efficacy of endobronchial autologous infusion of adipose-derived mesenchymal stem cells (ADMSCs) in patients with IPF.

Methods: We performed a prospective, non-randomized trial of endobronchial autologous ADMSCs in IPF patients who met ATS/ERS 2000 criteria with mild to moderate lung disease with IPF as assessed by Forced vital capacity (FVC)> 50% and diffusion capacity of the lung for carbon monoxide (DLCO) > 35%. All eligible
patients (n=14) underwent liposuspension and ADMSCs were isolated using a stan-
dard protocol provided by Adistem Ltd. ADMSCs were labelled with Technetium
(Tc-99m and endobronchially infused to both lower lobes. Tc-99m lung scanning
was performed to visualize infused cells. The primary end point was incidence
of treatment-emergent adverse events within 6 months after first infusion. FVC,
DLCO and 6-minute walking distance (6MWD) were exploratory efficacy end
points. 

Results: No cases of clinically significant allergic reactions, disease acute ex-
carceration or infection were recorded in all patients. There were no significant
alterations in FVC and DLCO 6 months post-treatment, though an almost marginal
trend towards improvement in 6MWD (P=0.07) was reported.

Conclusions: This ongoing clinical trial provides pivotal safety and provisional
efficacy data for endobronchial autologous infusion of ADMSCs in patients with
IPF. Larger studies are sorely needed.

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Effect and safety of mycophenolate mofetil in idiopathic pulmonary fibrosis. A retrospective study
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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrictic intersti-
tial lung disease with poor prognosis and treatment yet ineffective. Mycophenolate
Mofetil (MMF) is an immunomodulatory drug, acts by inhibiting lymphocyte
proliferation and is commonly used to prevent rejection following organ
transplantation.

Objective: We sought to determine the safety and efficacy profile of MMF in IPF
patients.

Methods: We retrospectively identified ten patients, all males, who met the
ATS/ERS 2000 criteria for IPF and received MMF 1.44g/d for 12 months. All of
them had inpatient hospital, pulmonary function and radiological (high reso-
lution computed tomography-HRCT) data available and therefore were enrolled
in the study. Forced vital capacity (FVC), total lung capacity (TLC), diffusion
capacity of the lung for carbon monoxide (DLCO), 6-minute walking distance
(6MWD), alveolar-arterial gradient of oxygen tension (PA-aO2), HRCT scans and
routine laboratory data at treatment onset were compared with respective values
12 months after treatment onset.

Results: There were no significant alterations in FVC, TLC, DLCO, 6MWD and
PA-aO2 pre- and 6 and 12 months post-treatment. HRCT evaluation showed a mod-
edeterioration of the total extent of disease (p=0.002). No cases of clinically
significant infection, leukemia, or elevated liver enzymes were recorded.

Conclusions: The above data suggest that MMF is a safe therapeutic modality
which resulted in overall stable disease regarding functional status while it demon-
strated a moderate progression as assessed by radiological parameters in a small
cohort of IPF patients. Larger, prospective studies are sorely needed.

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Late-breaking abstract: Evaluation of CRP, PCT, clinical pulmonary infection score and pneumonia severity scores for the diagnosis and prognosis of nursing home acquired pneumonia
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Introduction: Nursing home acquired pneumonia (NHAP) represents a distinct
group of respiratory infections with different risk factors, clinical presentation
and higher mortality than COP.

Aim: To evaluate the diagnostic value of clinical pulmonary infection score (CPSI),
CRP and PCT and compare the accuracy of CURB-65, pneumonia severity index
(PSI), nursing home acquired pneumonia (NHAP) index, SMART-COP and SOAR
in predicting in hospital mortality of NHAP.

Methods: 49 residents in nursing homes admitted to pulmonary department were
enrolled in the study. Pneumonia severity scores were recorded. CRP and PCT were
measured by immunonephelometry and immunoincromatography respectively.

Results: 39 patients were diagnosed with NHAP (group A) and 10 with other
pulmonary disorders (group B). Mean ± SE CRP was 16.3±1.65mg/dl in group A
and 2.6±2.56mg/dl (p=0.002) in group B. Mean ± SE PCT was 1.78±0.39mg/ml
in group A and 0.5±0.09mg/ml (p=0.001) in group B and mean ± SE CPIC was
5.7±0.18 in group A and 2.6±0.51 (p<0.001) in group B. The in-hospital mortality
was 17.9% in group A. PCT and CRP were accurate in predicting mortality with
AUC of 0.8 (95%CI 0.61-0.98) and 0.67 (95%CI 0.41-0.92) respectively. SMART-
COP, SOAR and PSI performed similarly with AUC 0.38 (95%CI 0.17-0.76), 0.52
(95%CI 0.3-0.75) and 0.57 (95%CI 0.36-0.77) respectively, whilst CURB65 [AUC
0.66 (95%CI 0.45-0.86)] and NHAP index [AUC 0.6 (95%CI 0.39-0.8)] showed
superior accuracy in predicting mortality.

Conclusions: The CPSI, PCT and CRP are reliable for the diagnosis of NHAP.
PCT, CRP and CURB65 were accurate for predicting in-hospital mortality in
patients with NHAP.

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COPD case finding in primary care: A pilot study in the West Midlands, UK
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Aim: To compare the effectiveness of targeted versus opportunistic case finding
for COPD in primary care.

Background: COPD is an increasing cause of morbidity and mortality, and un-
derdiagnosis is common. The recent draft Clinical Strategy for COPD for the UK
NHS recommended piloting case finding

Methods: Patients from two general practices, aged between 35 and 79 years with
a smoking history and no prior diagnosis of COPD or asthma were randomised
to either a targeted or opportunistic case finding arm. Patients in the targeted
arm were posted a respiratory questionnaire. Those in the opportunistic arm
received a questionnaire when they next presented at their general practice over a
6 month period. Patients with positive symptoms were invited to attend spirometry.
Those with an FEV1 predicted<80% and an FEV1/FVC<0.7 were diagnosed with
airway obstruction and referred to their GP or specialist respiratory nurse.

Results: 351 (32.7%) of 1073 distributed questionnaires were returned. 247 (70%)
of the patients who responded to the questionnaire were symptomatic. Of those
who underwent spirometry 14.3% were identified with airway obstruction. 10 out
of 815 patients (1.23%) contacted in the targeted arm and 4 out of 258 (1.55%) in
the opportunistic arm were identified with airway obstruction (difference 0.32%,
95% CI -1.37%, 2.01%). Overall 77 patients had to be contacted to identify one
patient with airway obstruction; 82 in the targeted and 65 in the opportunistic arm.

Conclusion: 17 more patients had to be contacted in the targeted than in the op-
portunistic arm to identify one patient with airway obstruction in this pilot. Further
work is needed with a wider range of practices to determine which approach is
more efficient.

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High rates of over-treatment of COPD in primary care: What risks to patients and costs to health services?
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Introduction: GOLD guidelines recommend inhaling medications for COPD based
on disease severity. Under-treatment denies patients the benefits of effective ther-
apy. Over-treatment with inhaled corticosteroids (ICS) risks side-effects including
both local and increased risk of pneumonia, in combination with long-acting bron-
dilators they also incur considerable financial waste. This study assessed adherence
to GOLD guidelines in primary care prescribing of inhaled COPD medication in
South-East London.

Methods: Data on management of COPD patients were extracted in 65 general
practices in Lambeth and Southwark including spirometry, inhaled medications
and recent COPD exacerbations. Patient severity was classed by GOLD stage and
appropriateness of prescribing was assessed.

Results: 4804 COPD patients were identified. Spirometry was recorded for 2941
(61%), of whom 778 did not meet GOLD diagnostic criteria. 2163 (45%) were
inappropriately treated according to GOLD. The most common deviation was over-prescription of ICS in GOLD II (55%), or III/IV with no history of severe exacerbations (56%). 793 (64%) cases of over-treatment involved LABA+ICS with a mean cost of £46.52/item.

Conclusion: Diagnosis of COPD was made without spirometry in the majority of
COPD patients in primary care. Deviation from GOLD in prescribing is substantial.
The potential for harm due to ICS over-prescription in over half of patients with a
confirmed diagnosis of COPD must give considerable cause for concern, besides the
unjustified costs.

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Missed opportunities to diagnose COPD
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Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of death in the world. Delay in diagnosing COPD appears common even among patients diagnosed in secondary care. Retrospective study of 95 cases

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Although a PFM is a useful tool for diagnosis and management of asthma, there are no such reference values for the adult Indian population. The aim of this study was to derive a predicted equation for PEF for Indian adults using an EU scale PFM.

Methodology: 5 centres representing different geographic, ethnic and socioeconomic backgrounds from India were selected (North: Srinagar, West: Jaipur, East: Kolkata, Centre: Pune and South: Hyderabad). Respiratory health and demographic questionnaires were administered to randomly selected 1000 rural and 1000 urban adults from each centre. Sampling was stratified according to gender, height and age. PEF values were measured using Breathometer (Cipla Ltd., India). The predicted equation was generated using linear regression analysis with SPSS software, Version 16.

Results and conclusion: Out of 9746 participants, 3608 were excluded as unhealthy based on presence of respiratory symptoms, smoking status and/or previous respiratory disease. 80% of the 6138 healthy adults (M: 3720; F: 2418) were used to derive the predicted equation. The equation was validated by comparing the predicted PEF values with the measured values in the remaining 20% sample. Using regression analysis, the predicted equations derived in L/min are: F: PEF = 168.551 – 1.776age + 1.354height; M: PEF = 69.259 – 2.296age + 2.888height. These reference PEF values for Indian adults are 24% lower for males and 27% lower for females than the Caucasian population.

Effectiveness of continuity in “World Day of COPD” awareness campaign on case finding for COPD in target population

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Background and aim: To evaluate effectiveness of continuity in awareness disease campaign on case-finding for COPD in a target population: over 35, smokers/ex-smokers, at least one respiratory symptom. Methods: 1-week marketing campaign was conducted 2009-2010 in WCD, using different marketing tools. Target population had open access to spirometry. Population was encouraged to visit COPD web-site to inform and take on-line COPD risk-test. In 2009-high visibility posters, leaflets within medical offices, 1-week marketing campaign was conducted 2009-2010 in WCD, using different marketing tools. Target population had open access to spirometry. Population was encouraged to visit COPD web-site to inform and take on-line COPD risk-test. In 2009-high visibility posters, leaflets within medical offices, press conference on World COPD Day. In 2010-media campaign, press conference preceded COPD Week, leaflets as personal letters from President of Romanian Society of Pneumology, distributed directly to population,through telephony companies. Primary outcome was number of COPD diagnosed. Secondary outcomes measures: unique site visitors, number of persons who perform on-line COPD risk test. Results: In 2009, 3494 persons were tested, 847 diagnosed (24%). In 2010, 4298 persons were tested, 1259 diagnosed (29%) – see Table 1.

Table 1: Outcomes testing for COPD campaign 2010 versus 2009

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>2009</th>
<th>2010</th>
<th>Growth 2010/2009 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested</td>
<td>3249</td>
<td>4298</td>
<td>32.29</td>
</tr>
<tr>
<td>New COPD diagnosed</td>
<td>747</td>
<td>1259</td>
<td>68.54</td>
</tr>
<tr>
<td>Diagnosis rate (%)</td>
<td>23</td>
<td>29</td>
<td>26.08</td>
</tr>
</tbody>
</table>

Conclusion: Continuity in awareness disease campaign on COPD case-finding

Effectiveness of the Wells score for pulmonary embolism diagnosis in primary care. Retrospective study of 95 cases

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Pulmonary embolism (PE) is an insidious life-threatening condition and its diagnosis represents a challenging topic in daily clinical practice since early recognition with appropriate management is known to improve prognosis. Clinical scores like Wells score are not used in daily practice by general practitioner (GP) and PE is most often diagnosed in hospital emergency room. We conducted a monocentric retrospective study which main objective was to evaluate the failure-rate and the efficiency of the strategy used by GP for PE diagnosis. All patients hospitalized for acute PE in a non-teaching hospital of the north of France were considered.

Ninety five patients were included. Retrospective evaluation of the Wells score gave a low PE probability in 34.7% and a strong or intermediate probability in 65.3% of the population whereas PE diagnosis was assessed by GP in 12% and 3%, respectively. We concluded that using the Wells score in general practice may improve the rate of PE diagnosis. To facilitate the implementation of such score, we developed an algorithm based on presence of dyspnea, thoracic pain or tachycardia that led to a 88% PE diagnosis by GP.

Usefulness of the Wells score for pulmonary embolism diagnosis in primary care. Retrospective study of 95 cases

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Prediction model for asthma in primary care. Retrospective study of 95 cases

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Background: Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of death in the world. Delay in diagnosing COPD appears common even though current consensus guidelines emphasize the importance of early detection.

Aim: To evaluate the effectiveness of a 2-stage-screening programme in primary care.

Methods: Subjects aged 65+ registered with a general practitioner (GP) in eastern Copenhagen received a simple questionnaire asking for smoking status and symp-
44. Smoking cessation science

187 Late-breaking abstract: Long-term efficacy of intensive behavior interventions and free medications for smoking cessation in Brazil

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Introduction: Treatment of tobacco dependence is associated with low long-term success rates, particularly in women. Our public clinic (NATTAB) offers intensive behavior interventions (IBI) program combined with free medications in Salvador.

Purpose: To evaluate the long-term tobacco abstinence rates and gender differences in success with free medications.

Methods: We evaluated consecutive smokers, clinical and psychologically, verified the Fagerström’s test (FT) score and offered IBI by a multidisciplinary team in group sessions (weekly x 4; then biweekly x 4 and monthly x 9). Coping skills and problem solving activities were developed. The rates of reported abstinence were evaluated by telephone contact or review of last visit on clinical charts, and compared by chi-square test.

Results: 467 patients were evaluated in 35 months, 330 initiated IBI, 85% of the patients used medications and had follow up for 14±11 months (67% for 12 months). Mean age was 53±10 yrs, 67% were women and median FT score was 6 (IQR 3). 79% of women and 75% of men quit smoking at some point. The abstinence and relapse rates were respectively: 51% and 31% at 1-3 mo; 50% and 36% at 3-6 mo; 48% and 39% at 6-12 mo; 44% and 41% at 12-24 months and 42% and 42% at 24-35 months. Abstinence rates did not differ for men and women (45% vs. 51%, p=NS, respectively). Among those who relapsed, the mean time of abstinence was 3.6±4.1 months, and they stated that abandoning the IBI sessions contributed to relapse.

Conclusions: Programs combining IBI with free medications can be effective for long-term smoking cessation despite moderate to high nicotine-dependence, independently of gender.

188 Smoking prevalence and willingness to quit in newly screened Danish patients diagnosed with airway obstruction

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Background: 436,000 Danes have chronic obstructive pulmonary disease (COPD) with one third diagnosed and treated with free medication. The Danish National Board of Health (NBH) recommends early detection of COPD focusing on: Age above 35 years. At least one pulmonary symptom. Smokers/ex-smokers or occupational diseases. Based on simulations, the timing of SCT initiation is critical to optimize health benefits and to reduce costs of care.

Aims and objectives: To evaluate the smoking prevalence and willingness to quit smoking in a population of newly diagnosed patients with airway obstruction in primary care in Denmark.

Methods: Following the recommendations by the NBH, participating GPs (n=335; 10% of Danish GPs) offered consecutively spirometry to patients with no previous diagnosis of obstructive. Demographic, spirometry, smoking status, smoking history and willingness to quit was recorded. The population indicated having COPD, was assessed as smoking status and smoking cessation initiatives.

Results: 3498 patients had spirometry, 1295 patients (37%, 61 years, 48% females) diagnosed with obstructive (FEV1/FVC < 70%). With more men than women (P=0.03) in total 64%, diagnosed with obstructive smoking (37 pack years, 17 cigarettes/day). 66% of smokers had a history of cessation attempts and 54% had used medication as part of the SC. 62% of the smokers like to quit, but only 11% intended to start immediately.

Indicated COPD severity and willingness to quit was not correlated.

Conclusions: Many patients identified with airway obstruction, indicating COPD, are current smokers. There is willingness to quit smoking, but only a few intend to initiate SC immediately, though guidelines recommend smoking cessation as primary intervention.

189 Predicted health and economic benefits of smoking cessation incorporating multiple quit attempts over a lifetime

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Objective: To evaluate the impact of age at start of smoking cessation treatment (SCT) on predicted health benefits and costs over smokers’ lifetime.

Methods: A discrete event simulation of SCT allowing multiple quit attempts and estimates of lifetime health and economic outcomes was developed in a U.S. population. SCT types were assigned based on observed use.

Results: The predicted life expectancy of the 18 to 74 years old (mean age 42.1 years) reference population was 26.8 years, corresponding to 13.9 discounted quality adjusted life years (QALY). The lifetime cost of SCT averaged $1,462, with a total direct cost (IDC) of smoking-attributable disease of $54,550/smoker. Smokers averaged 7.9 QALYs; 66.2% were permanent abstainers at the time of death. Smokers who started SCT at 35 to 40 years of age, accrued 15.6 discounted QALYs, and 74% achieved permanent abstinence. Smokers who started SCT between 50 and 55 years of age accrued 11.5 discounted QALYs and 60.2% achieved permanent abstinence at the time of death. Total abstinence times (IAT) were 10.1 vs. 7.2 years in the younger and older age groups, respectively, with corresponding SCT costs of $1,042 vs. $1,385 and lifetime IDC of disease of $43,306 vs. $72,439/smoker.

Conclusion: The number of individuals achieving permanent abstinence at the time of death is greater if smokers make their first quit attempt at age 35-40, rather than at age 50-55. Despite longer survival times, their costs are lower. The lifetime cost of SCT is negligible compared with the IDC of smoking-attributable diseases. Based on simulations, the timing of SCT initiation is critical to optimize health benefits and to reduce costs of care.

190 Long term predictors for smoking cessation in a long-term, population study at the workplace

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We implemented a voluntary, intensified, structured smoking cessation program with combined medical therapy for health care and health industry employees at workplace. 703 smoking employees from three sites assembled a 2 year program. This consisted of 10 visits with intensified counselling and motivational support. Various modalities of both nicotine replacement therapy and self-help programs were prescribed. Primary endpoint was nicotine abstinence at 12 and 24 months, which was defined as self reported abstinence confirmed by exhaled CO< 6 ppm. Predictive factors of nicotine abstinence were analyzed by multivariate regression analysis. Smoking cessation rates reached 38% after 12 months and remained unchanged after 24 months. Predictors of a successful quit attempt were higher education level (1.86 95% CI 1.12-3.07; p=0.016) and breathlessness at baseline (OR 2.53 95% CI 1.81-3.52; p<0.001). More severe nicotine dependency (OR 0.76 95% CI 0.59; 0.97; p<0.003), higher craving scores (OR 0.75 0.64-0.89; p=0.001) were negative predictors for successful quitting.

Conclusion: Smoking cessation intervention achieved high and stable longterm abstinence rates. Predictive factors for smoking cessation could be helpful to increase the effectiveness of smoking cessation programmes.
191 Smoking cessation effectiveness in smokers with obstructive respiratory disease

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Cigarette smoking is the major risk factor for the development of Chronic Obstructive Pulmonary Disease (COPD) and is associated with increased morbidity and reduced sensitivity to medication in asthmatic patients.

The aim of the present study was to evaluate the effectiveness of smoking cessation treatment in a sub-population of smokers with COPD and asthma in real life conditions and to compare the efficacy of three specific pharmacological agents.

A total of 2139 adults, current smokers were enrolled in the study. 298 subjects

Table 1. Abstinence rates in the three treatment groups in respiratory patients are shown in table 2

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>At the end of treatment</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control smokers</td>
<td>55.6%</td>
<td>52.4%</td>
<td>39.4%</td>
</tr>
<tr>
<td>COPD-Asthma</td>
<td>60.9%</td>
<td>55.1%</td>
<td>39.3%</td>
</tr>
</tbody>
</table>

The abstinence rates for the three treatment groups in respiratory patients are shown in table 2

Table 2. CAR in respiratory patients in different treatment groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>NRT (n=61)</th>
<th>Bupropion (n=79)</th>
<th>Varenicline (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the end on treatment</td>
<td>50.0%</td>
<td>56.2%</td>
<td>75.6%</td>
</tr>
<tr>
<td>6 months</td>
<td>55.3%</td>
<td>54%</td>
<td>66.7%</td>
</tr>
<tr>
<td>12 months</td>
<td>46.7%</td>
<td>57.3%</td>
<td>47.8%</td>
</tr>
</tbody>
</table>

Conclusion: Smoking cessation treatments are highly effective in smokers with respiratory co-morbidity as asthma and COPD and it can be achieved with all approved pharmacological agents through a personal approach, motivation and intensive follow-up program.

192 Smoking cessation treatment for COPD smokers

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We reviewed medical histories of all COPD patients who were treated in our Unit between January 2004 and 2010. All patients received both psychological and pharmacological treatment (NRT, varenicline or bupropion). Medical and smoking histories were obtained during the baseline visit. A Quit date was chosen and therapy was begun. In all follow-up visits, patients received treatment, and control of abstinence and monitoring of adverse effects were carried out. The treatment was free of charge. The assessed outcomes were continuous abstinence rate (CAR) between week 9 and 12 and CAR between week 9 and 24, both defined by not smoking over those periods of time. Levels of CO of 10 ppm or less were required.

The average rate on FTND-questionnaire was 7.4 (2.1), NRT was prescribed in 233 (49%), Bupropion in 45 (9.5%), Varenicline in 196 (49%), and 4 (1.5%) of them did not receive treatment. Global effectiveness was: CAR from week 9 to 12 was met by 54.3%, and CAR from week 9 to 24 was met by 48.5%. Taking into consideration the kind of treatment used, CAR from week 9 to 24 were 44.1%, 60% y 61% for nicotine patches, bupropion and varenicline respectively. Significant differences were observed between varenicline and nicotine patches. OR: 1.98 (1.25-3.12); p.<0.001.

Good effectiveness of pharmacological treatments for COPD smokers. Good safety pattern of smoking cessation pharmacological treatments for COPD smokers.

Varenicline gets better efficacy results than nicotine patches in this group of smokers.

193 A placebo-controlled trial with varenicline for long term nicotine replacement product users

Philip Tonnesen, Kim Mikkelsen. Palm Dept, Gentofte Hospital, Copenhagen, Denmark Palm Dept, Gentofte Hospital, Copenhagen, Denmark

In this placebo, controlled trial we enrolled 139 long-term users of nicotine replacement products (NRT) (>1 year) to either varenicline (N=70) or placebo (N=69) for 3 months combined with 9 visits with counselling by nurses. The primary outcome showed that the varenicline group had a higher quit rate with NRT compared with placebo, statistical significant after 12 and 16 weeks but borderline significant on most other measure points. After 1 year the NRT quit rate was 19% vs. 36.2%, respectively. A Mantel-Haenszel test over all visits showed significant superiority for active therapy vs. placebo, odds ratio 1.83 (95%CI: 1.43-2.35), P<0.0001. Results for withdrawal symptoms, adverse events from varenicline, and weight changes will be reported. Also, changes in total-cholesterol, LDL, HDL and triglyceride after 3 and 12 months will be reported for NRT quitters and failures as well as changes in p-cotinine for users of NRT.

This is the first study reporting data for varenicline to be used for long-term NRT users. The study seems to be underpowered but overall the findings showed superiority for varenicline vs. placebo.

In conclusion, this study shows that varenicline seems to be a drug that might be effective in getting long-term NRT users to quit.

194 Efficacy and safety of a novel nicotine mouth spray in smoking cessation: A randomized, placebo-controlled, double blind, multicenter study with 52-week follow up

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The study was a randomized (2:1) double-blind, placebo-controlled, low-intensity counseling study of the efficacy of a novel nicotine mouth spray (1 mg/spray) and its aid to smoking cessation. The study enrolled daily cigarette smokers aged 18 years or older, who were motivated to quit and who had a CO level of >10 ppm. During Weeks 1-6, they were instructed to use 1-2 sprays whenever they would normally have smoked a cigarette, or whenever they experienced cravings to smoke, up to a maximum dose of 4 sprays per hour, and 64 sprays per day. The dose was tapered down during Weeks 7-12. Low intensity counselling was provided during the study.

Continuous CARverified abstinence rates (CAR) were measured from Week 2 and were statistically significantly higher with active treatment than placebo. CAR after 6 weeks and 52 weeks were 26.1% vs 16.1% and 13.8% vs 5.6% (RR: 2.48, 95% CI: 1.24-4.94) for active vs placebo, respectively.

Treatment-related adverse events were common with both active and placebo, and were reported by 87% of subjects who used active spray and 71% of subjects who used placebo spray. Most adverse events reported were mild to moderate, and only 9.1% of participants in the active group and 7.5% in the placebo group withdrew due to adverse events.

In conclusion, these findings show that the nicotine mouth spray is a well-tolerated and effective aid to smoking cessation. At one year, the OR for sustained abstinence with active spray versus placebo was 2.7, and the RR was 2.5. Adverse events were common with both active spray and placebo, but were mostly mild to moderate, and generally tolerated.

45. Mechanisms and outcomes of infective exacerbations of COPD

195 Late-breaking abstract: Moxifloxacin (MXF) vs amoxicillin/clavulanic acid (AMC) in acute exacerbations of COPD (AECOPD): Results of a large clinical trial with a novel endpoint

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Introduction: Evidence-based therapy of AECOPD is limited by a lack of appropriate trials. MAESTRAL compares antibiotic therapies for AECOPDs in patients with moderate-to-severe disease at risk of poor outcomes.

Method: This was a multiregional, prospective, randomised, double-blind study of patients ≥60 years, FEV1<60% predicted, with an Anthonisen type 1 exacerbation and ≥2 exacerbations in the last year. Patients were stratified by systemic steroid use and received MXF 400 mg PO qd (5 days) or AMC 875/125 mg PO bd (7...
Rhinovirus infection induces secondary bacterial infection in COPD

Patrick Mallia1, Joseph Footitt1, Rosa Sotero1,3, Annette Jepson1

Rhinovirus infection induces secondary bacterial infection in COPD

Results: Both drugs had good efficacy. At the 8-week endpoint, MXF was superior to AMC in microbiologically confirmed AECOPD. Bacterial eradication and clinical success were strongly correlated. The results may help physicians optimise antibiotic therapy in moderate-to-severe AECOPD.

Conclusion: Both drugs had good efficacy. At the 8-week endpoint, MXF was superior to AMC in microbiologically confirmed AECOPD. Bacterial eradication and clinical success were strongly correlated. The results may help physicians optimise antibiotic therapy in moderate-to-severe AECOPD.

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Rhinovirus infection induces secondary bacterial infection in COPD

Patrick Mallia1, Joseph Footitt1, Rosa Sotero1,3, Annette Jepson1, Gregory Oleszkiewicz1, Julia Aniscenko1, Onn Min Kon1, Papi Alberto3, Albert Gabarrús, Antoni Torres

Rhinovirus infection induces secondary bacterial infection in COPD

Methods: We performed experimental rhinovirus (RV) infection in COPD subjects (GOLD stage II, N=20), smokers with normal lung function (SMK, N=21) and non-smokers (NS, N=11). Sputum was collected at baseline and following inoculation. RV infection was confirmed with PCR and semi-quantitative bacterial culture performed. SLPI, elafin and neutrophil elastase (NE) were measured in sputum by ELISA.

Results: 1 subject with bacteria in baseline sputum was excluded. Following RV infection bacteria were detected in 65% of COPD, 19% of SMK and 30% of NS (P=0.0086). 92% of bacteria in the COPD group were pathogenic bacteria, compared with 50% in SMK and 33% in NS (P=0.045). Peak sputum virus load was on day 5 and peak bacterial load on day 15. Following RV infection sputum SLPI and elafin fell from baseline in the bacteria+ve subjects and increased in the bacteria−ve subjects.

Peak virus load (4.4±0.72 vs 6.5±0.66 copies/mL,P=0.049) and sputum NE on day 0 (0.65±0.14 vs 0.31±0.07μg/mL,P=0.026) were higher in subjects with bacterial infection compared to those without.

Conclusions: Secondary bacterial infection is common following rhinovirus infection in COPD and is associated with higher virus loads and NE, but lower levels of SLPI and elafin in sputum. Degradation of SLPI and elafin by NE may be a mechanism of increased susceptibility to bacterial infection.

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Predictors of poor outcome in severe hospitalised COPD exacerbations

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Background: The aim of study was to determine predictors of poor outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease (ECOPD).

Methods: Hospitalised patients with ECOPD were included in a prospective study and followed for 1 month. Clinical and epidemiological parameters were evaluated including COPD Severity Score (COPD-SS) and Charlson Index. Poor outcome was death, intensive care unit (ICU) admission, need for mechanical ventilation (MV), prolonged hospital stay (>11 days) and emergency room (ER) visit/re-admission during follow-up.

Results: 155 patients: mean age:41±standard deviation 9.6 years; 84% men; 76% smokers/ex-smokers; 55% GOLD stage III or IV; mean hospital stay 8±5 days. Cox proportional hazards model showed that previous exacerbations, hospitalisation for ECOPD and COPD-SS were independently associated with poor outcome: exacerbations and hospitalisation for ECOPD in the last year (p=0.033 and 0.039 respectively); lower FEV1 (p=0.004); GOLD stageII (p=0.049); lower pH (p<0.001); lower PaO2/FIO2 (p=0.006); higher PaCO2 (p<0.001); higher COPD-SS (p=0.016); long-term O2 therapy (p=0.042). Independent predictors of poor outcome determined by multivariate analysis: number of exacerbations in the previous year (1 ECOPD: p=0.012, odds ratio [OR] 4.1, 95% confidence interval [CI] 1.4 to 12.3; ≥2 ECOPD: p=0.005. OR 4.4, 95% CI 1.6 to 12.5); pH (p=0.006, OR 0.2, 95% CI 0.1 to 0.7); PaCO2 (p=0.015, OR 1.3, 95% CI 1.1 to 1.7).

Conclusion: Previous exacerbations, hypercapnia and respiratory acidosis were identified as predictors of poor outcome in patients with severe ECOPD.

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Human respiratory epithelial cells acquire a long-lasting antiviral condition when exposed to interferon beta

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Type I interferons (IFNs) induce strong antiviral effects and are therefore attractive to prevent seasonal respiratory infections or reduce the incidence of virus-mediated exacerbation in COPD patients. Yet, clinical application of type I IFNs is hindered due to significant side effects observed during repetitive use. In this study we investigate the duration of protection, mediated by prophylactic IFNbeta, against a human rhinovirus (HRV) infection.

Human respiratory epithelial (A549) cells were exposed for 18 hours to various concentrations (31.500 IU/ml) of IFNbeta. Then, IFNbeta was either removed or maintained in the supernatant for the rest of the experiment. Next, cells were infected with HRV-IB (MOI 0.1) at t = 0, 24, 48, 72 or 168 hours after the initial exposure to IFNbeta. At 48 hours post infection, the protective effect of IFNbeta on HRV-induced cell death was determined by a colorimetric assay RT-qPCR and plaque assay were used to determine HRV infection. In the continuous presence of IFNbeta, 90-100% of A549 cells were protected against HRV-induced cell death at every time point and at all IFNbeta concentrations. This strong protective effect was confirmed by RT-qPCR and plaque assay. Alternatively, when IFNbeta was removed, cell death increased with time and in a dose-dependent way. Nevertheless, at 16th post IFNbeta stimulation (5000 IU/ml), still 75% of all cells were viable.

These data show that IFNbeta has not only a strong, but also long-lasting protective effect against HRV-IB. This opens new opportunities for prophylactic treatment of viral respiratory infections without the risk of side effects often seen after repetitive and systemic use.
Pentraxins are a family of acute-phase reactants and pentraxin-3 (PTX3) is the prototypic long pentraxin. PTX3 has a protective role against pathogens including influenza viruses and both pro- and anti-inflammatory actions of PTX3 are described. The role of PTX3 in virus-induced COPD exacerbations is unknown.

Methods: We infected 3 groups of subjects—COPD GOLD stage II (N=20), smokers with normal lung function (SMK,N=21) and non-smokers (NS,N=11) with rhinovirus (RV). Induced sputum was collected on 6 time points post-inoculation, cytospins prepared and cell counts determined. PTX3 and neutrophil elastase (NE) were measured in sputum supernatants by ELISA and sputum virus load by quantitative PCR.

Results: Following RV infection PTX3 in sputum was significantly increased over baseline in the COPD group and the SMK but not the NS.

Metagenomic analysis of lower airway microbial diversity in patients with chronic pulmonary disease

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1Pneumology Service, Corporació Parc Taulí. Sabadell, Barcelona, Spain; 2Genomics Service, Centro Supervisor de Investigación en Salud Pública, Valencia, Spain; 3Laboratory Service, IRCs Germans Trias i Pujol. Ciberes, Barcelona, Spain

Aim: To identify microorganisms unrecognized through culture in the lower airway of patients with chronic pulmonary disease through amplification and pyrosequencing of specific genes for microbial diversity assessment

Method: To avoid culture-related bias, 16S DNA extraction from respiratory samples (sputum, bronchial aspirate (BAS), bronchoalveolar lavage (BAL) and bronchial mucosa); 2) 16S rRNA amplification and purification with modified primers which were classified as probable IPA, possible IPA (n=6), colonization (n=2) and non-IPA group (n=17); According to the ROC curve, when chose 0.795 as the cut-off of BALF GM test, the sensitivity, specificity, positive and negative predictive value for probable IPA were 88.9%, 95.1%, 100% and 93.7%, respectively.All of the patients of IPA group were dead. The result of GM test in BALF with IPA group were much higher than control group (2.88 vs 0.49, p<0.001). The mortality was much higher in the patients whose GM test in BALF above 0.795 than the patients lower 0.795 (80% vs 17%; p=0.001).

Conclusions: Compare to serum GM and aspergillus culture, GM in BALF prove to be more useful in early diagnosis of IPA with critically ill COPD patients. 0.795 maybe a best cut-off in BALF GM detection. Besides, high GM value in BALF was associated with high mortality in a certain sense.

Reducing exacerbations in COPD with OM-85: A multicentre, double-blind, placebo-controlled trial

Dario Olivieri. Department of Clinical Sciences, University Hospital, Parma, Italy

Background: Acute exacerbations in COPD (AE-COPD) are a key driver of morbidity and mortality. They are mainly triggered by respiratory infections. OM-85 is a bacterial lysate by immunostimulating properties already known to reduce AE-COPD.

Aims and objectives: Confirm and further investigate the efficacy and safety of OM-85 (Broncho-Vaxom®, Broncho-Munal®, Ommunal®) with a specific dosage regimen in reducing the rate of acute exacerbations in moderate to severe COPD patients.

Method: This randomised, placebo-controlled, double-blind, multicentre trial was performed with 340 patients from 5 countries, past or active smoker, over 40 years old, with COPD stage II or III, with a history of at least 2 documented AE-COPD in the previous year, and a FEV1 between 30% and 80%.

Results: Preliminary results show that OM-85 significantly reduced the rate of AE-COPD by 35.4% after the 5 months treatment period (p=0.0155). The mean duration of AE-COPD was significantly decreased by 1.4 days in the OM-85 group (1.5 vs 2.9 days; p=0.0498). The rate of treatment-emergent adverse events (TEAEs) was similar in both treatment groups (OM-85: 44.1%, placebo: 43.3%).

Conclusion: OM-85 significantly reduced the rate and duration of AE-COPD in moderate to severe COPD patients. Safety and tolerance were excellent.

SUNDAY, SEPTEMBER 25TH 2011
Conclusion: Current regression equations to estimate Wpeak based on 6MWD in COPD are inaccurate in COPD. So, estimated Wpeak cannot be used to target treatment intensity during PR in individuals with COPD.

205 Divergent effects of obesity on weight bearing versus non-weight bearing exercise testing in patients with COPD

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Introduction: Obesity is common in patients with COPD and may impact on disease severity. However, obesity was not associated with diminished exercise capacity or greater dyspnea during non-weight bearing exercise (e.g. stationary cycling) in COPD1. Aim of this study was to investigate the impact of obesity during weight bearing exercise (e.g. six-minute walk test, 6MWT) in patients with severe COPD.

Methods: Data obtained during pre-rehabilitation assessment of 44 male obese COPD patients (OB) (age 58±6y, FEV1% pred= 39±10), BMI 23.0±1.2 kg/m². 6MWT and progressive cycle ergometry (CPET) were performed, BORQ scores for dyspnea and leg fatigue were recorded at the end of both tests.

Results: Distance of 6MWT was significantly reduced in OB (452±101 m) compared with NW (497±82 m, p<0.05), while peak cycling exercise load was comparable (OB 90±11 W, NW 85±24 W, ns). Dyspnea (5.9±2.0 vs. 4.9±2.0, p<0.05) and leg fatigue (4.8±2.4 vs. 3.4±2.2, p<0.05) sensations after 6MWT were significantly increased in OB compared to NW, while these were comparable after CPET (dyspnea: OB 7.6±1.8 vs. NW 7.4±2.0, ns; leg fatigue: OB 6.1±2.2 vs. NW 6.3±2.5, ns).

Conclusion: In contrast to non-weight bearing exercise, obesity has a negative impact on weight bearing exercise capacity and exercise-related symptoms in male patients with severe COPD. Obese COPD patients may prefer cycling instead of treadmill walking as training modality during rehabilitation.

04 Tru et al, Combined effects of obesity and COPD on dyspnea and exercise tolerance, Am J Respir Crit Care Med 2009

206 Investigating circulating microRNAs as potential biomarkers of quadriiceps weakness in COPD

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Introduction: Non-invasive biomarkers of quadriiceps phenotype in COPD are needed. MicroRNAs (miRs) are small non-coding RNA that modulate gene expression. They circulate in blood as exosomes and are promising biomarkers. We hypothesised that muscle specific miR-499, which controls slow myosin expression, would be differentially expressed and correlate with physiological parameters.

Methods: We studied 101 COPD patients and 24 controls. MiR-499 was quantified in stored plasma samples using qRT PCR1. Mir-16 and mir-222 were quantified as negative controls. Results were normalised to a spiked-in control. All subjects had paired quadriceps biopsy samples.

Results: Characteristics as mean (SD): COPD patients: 66 M: 35 F, age 68 (± 6), FEV1% pred= 44 (±19), six-minute walk (6MWW) = 394 (±121). Controls: M 14: T 10, F, age 68 (± 6), FEV1% pred= 112 (±13), 6MWW= 616 (±83).

Systemic inflammation is an important factor in skeletal muscle dysfunction (SMD) in chronic obstructive pulmonary disease (COPD) patients. The SMD can be reversed partially by physical training; however, the response is dependent of type, intensity and duration of exercise. This study evaluated the inflammatory response, muscle strength and fat-free mass outcomes in COPD patients comparing two protocols of resistance training. COPD (n=34) were assigned to conventional resistance training (CRT) or elastic tubing training (ETT) groups (n=17 each, FEV1= 1.23±0.46% and 1.24±0.54% predicted; aged 64±11.7 y, respectively). CRT group were trained at moderate intensity (3×10 RM) and ETT group were trained at 2-7 sets of repetitions determined individually by resistance to fatigue test. TNF-α, cytokines (IL-1β and IL-10) on plasma by ELISA, peripheral muscle strength and fat-free mass were obtained at baseline (D0) and after the 8-weeks training intervention (D2). Citokines also were measured acutely immediately after the first (D1) and the last training session (D3). TNF-α, IL-1β and IL-10 increased in CRT group after 8 weeks compared to baseline (p<0.001), p<0.05 and p<0.001, respectively). IL-1β and IL-10 levels also increased in response to acute exercise (D1) and IL-10 measured acutely after 8 weeks training (D4) was reduced (p<0.01, compared to D3). No changes in cytokines levels in plasma were observed in the ETT group. Muscle strength increased in both groups, but only the ETT protocol increased the fat-free mass after 8 weeks. These findings suggest that structural and functional gains were obtained from a lower systemic cost in the ETT group.

208 Early peripheral muscle structural and metabolic impairment in chronic obstructive pulmonary disease (COPD) patients cannot be considered as a consequence of sedentary lifestyle

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Peripheral muscle dysfunction in COPD patients has been related to a muscle/fiber atrophy and oxidative metabolism reduction, which mimicks a severe disease. Thus, we investigated the structure and mitochondrial function in skeletal muscle biopsies from patients with COPD and sedentary healthy subjects (SHS). 24 stage I-II (according to the GOLD classification) COPD patients and 21 age-matched SHS (<150min/W of moderate-vigorous PA) had accelerometry recording, quadriiceps function and muscle (impedancemetry) assessment. All subjects had a biopsy of the quadriiceps, allowing assessment of the respiratory parameters and mitochondrial ATP synthesis, and of the muscle morphology (immunohistochemistry). Results are presented in mean ± SD or median [inter-quartile range]. COPD patient and PA level-matched SHS (activity counts/day: 133±70 vs 135±48; p=0.9), had the same muscle mass and fiber cross-sectional areas. However, there was a reduction of the quadriiceps endurance and of the type I fiber proportion (35% [28-49] vs 41% [38-53]; p<0.05). While the maximal ADP-stimulated respiration (state 3) with pyruvate substrate was comparable in COPD and SHS, the ATP/O value (ratio between ATP synthesis and oxygen consumption) was significantly reduced in COPD (0.96±0.04 vs 2.6±0.8; p<0.001), and observed in early stages. This study showed an early impairment of the muscle oxidative metabolism (type I fibers and mitochondrial efficiency), unexplained by the PA reduction in COPD. COPD past that the oxidative phosphorylation alteration (OXPHOS pathway) occurs in the PHOS plot, i.e. the ATP synthesis rate.
COPD patients often experience walking as a problematic daily activity. Although a rollator can improve mobility, many patients feel ashamed to use it. Therefore, other walking aids may be worthwhile to consider. We aimed to determine whether a new walking aid (fig 1a) has similar direct effects on 6MWD as a rollator (fig 1b) in COPD patients.

**Figure 1. A: Walking frame “City”, B: rollator.**

21 COPD patients (52% men; age: 64±11yrs; FEV1: 42±15% pred) performed 2 6MWTs during pre-rehabilitation assessment (mean best 6MWD: 369±88 m). In addition, 2 extra 6MWTs were randomly performed on 2 consecutive days: 1x with rollator and 1x with walking frame. Walking pattern (n=21) was determined using an accelerometer and metabolic demands (n=10) were assessed using a mobile oxycron.

Using walking frame resulted in a higher mean 6MWD (466±189 vs. 383±85 m) and fewer steps (491±122 vs. 601±298) compared to a rollator (all p<0.05). Oxygen uptake, ventilation, heart rate, oxygen saturation and Borg symptom scores were comparable. 19% felt ashamed using rollator compared to 10% using walking frame.

Functional exercise performance can be improved using walking aids in COPD patients. Moreover, using walking frame led to a significant improvement in 6MWD compared to using rollator, with the same metabolic demands. Therefore, the new walking aid may be a good alternative for a rollator in COPD patients.

This study was financially supported by “Stichting De Weijerhorst.”

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**Combining physical activity monitoring and cardiac output during exercise in COPD patients with GOLD stages II-IV**

Eleni Kortianou1,2, Ioannis Vogiatzis1,3, Zafeiris Louvaris1,2,1

1Respiratory Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom; 2Drug Discovery, AstraZeneca, Loughborough, United Kingdom

In COPD, alveolar macrophages (AM) increase, release more inflammatory mediators but respond poorly to glucocorticosteroids. Different macrophage phenotypes are identified in animals based on density but no definitive studies on human lung macrophages exist. Cells were isolated from resected human lung tissue from non-smokers (NS, n=5) smokers (S, n=11) and COPD (n=7) patients. Cells were separated into three viable fractions using Percoll density gradients (A: 30-40%, B: 40-50% C: 50-60%). Responses to budesonide after stimulation with lipopolysaccharide (LPS) were investigated by measuring TNFα, CXCL8 and IL-10 release by ELISA. Baseline and LPS-stimulated release of TNFα, CXCL8, and IL-10 did not differ between cell fractions or subjects. LPS-stimulated TNFα release from fraction A from NS and S were responsive to budesonide (EC50 NS: 0.5±0.04nM vs S: 1.8±1.1nM), with inhibition at 10M being ~80% (NS) and ~60% (S). However, COPD cells were unresponsive. Budesonide (10M) inhibited LPS-stimulated CXCL8 release from fraction A similarly in NS and S but less effectively in COPD cells (~30%, p<0.05) with EC50 values 0.6±0.1nM (NS), 1.0±0.3nM (S) and 2.4±0.9nM (COPD) cells. This apparent steroid insensitivity of COPD macrophages from fraction A was selective, as budesonide inhibited LPS-stimulated IL-10 release by ~55% in fractions A from S and COPD patients (EC25 S: 2.0±1.7nM vs COPD 1.7±1.1nM) but by 80% (EC50 S: 9.0±2.0M) in NS cells. TNFα and CXCL8 responses of cells from fractions B and C did not differ between subjects. Fraction A COPD macrophages were less responsive to budesonide and may represent AM. Identifying selective fraction A markers will allow development of directed therapies.

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**LSC 2011 Abstract: Production of alpha-1 antitrypsin (AAT) by pro- and anti-inflammatory macrophages and dendritic cells**

Emily F.A. van ’t Wout, Annemarie van Schadewijk, Nigel D.L. Savage, Jan Stolk, Pieter S. Hiemstra, Paul M. Thomas, Kinghorn Centre, Leiden, Netherlands; Infectious Diseases, Leiden University Medical Centre, Leiden, Netherlands

AAT acts as an important neutrophil elastase inhibitor in the lung. Although the hepatocyte is considered as the primary source of AAT, local production by monocytes, macrophages and epithelial cells may contribute to the formation of an anti-elastase screen. Since monocytes can differentiate into a heterogeneous population of macrophages with subpopulations ranging from pro-inflammatory properties (M1) to anti-inflammatory properties (M2), and into dendritic cells (DC), we studied whether lipopolysaccharide (LPS), TNFα and oncostatin M (OSM) enhance AAT production differentially in cultured M1, M2 and DC. Monocytes from healthy blood donors were cultured for 7 days in the presence of GM-CSF, M-CSF or GM-CSF + IL-4 to obtain M1, M2 and immature (i) DC, respectively. Next, cells were stimulated with LPS, TNFa or OSM and synthesis of AAT was assessed by quantitative RT-PCR and ELISA. Spontaneous release of AAT was higher in M1 than in M2 and iDC after 24h (187 ng/106 cells vs 50 ng/106 and 80 ng/106, p<0.016). LPS significantly increased AAT production in M1, M2 and DC (302 ng/106 vs 97 ng/106 and 248 ng/106, p<0.019), whereas TNFα and OSM did not affect AAT secretion. The secretion levels of the related protein inhibitor alpha-1 antichymotrypsin (ACT) were below the limits of detection by ELISA. Analysis by quantitative RT-PCR showed that 24h LPS exposure caused a maximal 2.1-fold AAT mRNA increase in M1, a 21-fold increase in M2 and 11-fold increase in DC.

We conclude that cultured M1 produce more AAT than M2 and DC, which is partly explained by a high spontaneous release of AAT by M1. This suggests that cellular differentiation is a regulator of local AAT production.
Background: Neutrophils are among the first cells to arrive at the site of injury and chemokine release by neutrophils is altered in COPD as compared to healthy controls. Neutrophils spontaneously release CXCL-8, CCL-2 and CCL-3. Inhibitors of neutrophils such as Ac-PGP significantly inhibit the release of LPS induced CXCL-8. There is growing evidence that Ac-PGP generated increased endogenous Ac-PGP when incubated with intact collagen; this effect was inhibited by an ERK1/2 pathway inhibitor.

Conclusions: These data indicate that ERM-dermed Ac-PGP released in MMP-9 activated from PMNs by the ligand of CXCR1 and CXCR2 and subsequent activation of the ERK1/2 MAPK, demonstrating a new pathway of matrix-mediated protease regulation and subsequent “feed-forward” Ac-PGP production.

216 JAK/STAT inhibition improves macrophage phagocytosis of bacteria

Rebecca A. Holloway1, Iain Kilty2, Peter J. Barnes 1, Louise E. Donnelly 1.

Introduction: JAK/STAT pathway is involved in host defence against infection with Gram-negative bacteria.

Methods: Using RAW264.7 murine macrophages and the human monocyte cell line THP-1, we examined the effect of inhibitors of JAK/STAT pathways (PF95, PF13) on phagocytosis.

Results: Both PF95 and PF13 increased phagocytosis by 2.4 and 12 fold, respectively. Co-incubation with IFN-γ + TNF-α increased phagocytosis by 3.3 fold, with a 1.8 fold increase at 48 h. Pre-treatment with JAK/STAT inhibitors did not affect phagocytosis.

Conclusion: JAK/STAT pathway inhibitors increase phagocytosis, suggesting that this pathway is involved in host defence againstGram-negative bacteria.

217 Increased expression of phosphodiesterase 4 (PDE4) A, B and D in alveolar macrophages from chronic obstructive pulmonary disease (COPD) patients

Simon Lea1, Aleksandra Metyka1, Fabrizio Facchini2, Dave Singh3.

Background: Phosphodiesterase-4 (PDE4) inhibitors, such as roflumilast, may offer novel anti-inflammatory strategies in respiratory diseases, including chronic obstructive pulmonary disease (COPD). Although it is widely accepted that PDE4 is expressed in macrophages, there is a lack of knowledge regarding the expression levels of PDE4 subtypes in alveolar macrophages (AM) from COPD patients.

Methods: We examined mRNA levels of PDE4A, B and D in AM from patients with COPD and the modulatory effects of roflumilast on LPS-evoked cytokine release.

Results: Expression of PDE4A, B and D were significantly augmented in AM from COPD patients compared to non-smokers (P<0.05). Roflumilast significantly (P<0.01) reduced LPS induced TNFα production in a concentration-dependent fashion (0.05-5 μM) while had no significant effect on IL-6 or IL-8 release.

Table 1. Results of PDE4 inhibitors on IFNγ suppression of bacterial production

<table>
<thead>
<tr>
<th>Drug</th>
<th>HI</th>
<th>SP</th>
</tr>
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<tbody>
<tr>
<td>PF95</td>
<td>EC50 μM</td>
<td>0.27±0.26</td>
</tr>
<tr>
<td></td>
<td>% increase</td>
<td>39±16</td>
</tr>
<tr>
<td>PF13</td>
<td>EC50 μM</td>
<td>2.5±2.4</td>
</tr>
<tr>
<td></td>
<td>% increase</td>
<td>36±17</td>
</tr>
</tbody>
</table>

Data are mean±SEM, n=5

Inhibiting the JAK/STAT pathway diminishes the decrease in phagocytosis of HI and SP caused by IFNγ and decreases the release of inflammatory cytokines and has potential as a novel target in COPD.

References:

1. Lea S, Metyka A, Facchini F, Singh D. Inhibition of PDE4 reduces LPS-induced cytokine release in alveolar macrophages from COPD patients.

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Data are mean±SEM, n=5

Inhibiting the JAK/STAT pathway diminishes the decrease in phagocytosis of HI and SP caused by IFNγ and decreases the release of inflammatory cytokines and has potential as a novel target in COPD.
Conclusion: mRNA levels of PDE4 A, B and D are increased in AM from COPD patients. Rosflumilast inhibits TNFα production from AM from COPD patients.

218 Cigarette smoking augments toll-like receptor 3 expression and responses in macrophages

Aikra Kourai, Satoro Yanagisawa, Hisatose Sugiri, Tomohiro Ichikawa, Keichiro Akamatsu, Tsunahiko Hirano, Masanori Nakashima, Kazuto Matsunaga, Yoshikazu Kinoshita, Masakazu Kinoshita. Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan

Toll-like receptor 3 (TLR3), which reacts to viral-derived double-stranded RNA, is suggested to be involved in the immune responses during viral infection. However, the role of TLR3-mediated response in the pathophysiology of chronic obstructive pulmonary disease (COPD) is unclear.

The expression of TLR3 in alveolar macrophages in human lung tissues was analyzed by immunohistochemistry. Furthermore, the effect of cigarette smoke on the expression and responses of TLR3 in macrophage lineage cells was examined. TLR3-positive macrophages were significantly increased in smokers and COPD subjects compared with non-smoker control subjects, but there was no difference between smokers and COPD subjects. The values of TLR3-positive macrophages were positively correlated with the smoking history and negatively correlated with the values of corrected carbon monoxide diffusing capacity by alveolar ventilation (DLCO/VA) (p < 0.001, r = -0.56), but not with the values of forced expiratory volume in 1 second (FEV1)% of predicted. Furthermore, cigarette smoke potentiated the expression of TLR3 in monocyte-derived macrophages and significantly augmented the release of interleukin-8 (CXCL8) and total matrix metalloproteinase-9 activity in TLR3 ligand-treated cells.

These data suggest that cigarette smoke potentiates the expression and responses of TLR3 in alveolar macrophages, which may affect the pathogenesis of COPD as well as its exacerbation.

48. Immunobiology in the transplanted lung: experimental and clinical evaluations

219 Late-breaking abstract: Non specific IgG replacement in lung transplantation recipients with low IgG plasma levels: Effects on survival and bronchiolitis obliterans syndrome incidence

Christophe Pison 1,2, Marion France 1, Hubert Roth 3, Christel Saint Raymond 1, Johanna Claustre 2, Boubou Camara 1, Sébastien Quétant 1, Grenoble Lung Transplantation Group 1, 1 Clinique de Pneumologie, CHU Grenoble, Université Joseph Fourier, Grenoble, France; 2 LBFA, Insen1055, Grenoble, France

After lung transplantation, IgG plasma levels < 6 g/L are recorded in more than 50% of cases resulting in adverse events [JHLT 2001:7242, Transplantation 2005;79:1723]. We conducted a open study with non specific IgG, Tegeline® in all patients with IgG plasma < 6 g/L post transplantation since 1991 in 59 out of 119 consecutive recipients more than 3 months in Grenoble. Both groups had similar donor and recipient characteristics and deaths a mean period of 2.1±1.3 years except for a shorter duration of ventilation in donors, a longer first hospitalization stay and more acute rejection/TBR performed 0.32±0.12 vs 0.11±0.18 in non-substituted group. IgG substitution started 4.5±0.76 months and lasted 5±0.115 months, mean cumulative doses were 53±48 gr. In multivariate Cox regression model, IgG substitution conferred a net benefit in terms of survival at 5 years HR: 0.40 (0.18-0.88) 95%CI p=0.022 taking in account age of recipients and donors, type IC rejection, number of treated infection and rejection episodes.

We conclude that replacement therapy with non specific IgG in lung transplant recipients with low IgG plasma levels resulted in a better survival and BOS free survival at 5 years post-transplantation as compared to non-substituted group. Limitation: non randomized design. A prospective controlled multicentre study is warranted. Funds from LBFA, France.

220 Significance of anti-HLA immunization in lung transplantation

Jérémie Rech 1, Pierre-Emmanuel Falcoz 2, Nicola Santelmo 1, Ziad Mansour 2, Romain Kessler 1, Gilbert Massard 1.

1 Emergency, Grenoble University-Affiliated Hospital, Grenoble, France; 2 PRETA, Laboratoire TIMC-IMAG, La Tronche, France

Rationale: The ex vivo pulmonary perfusion is a suitable method of evaluation of lung ischemia reperfusion injuries (IRI). The role of the Cyclosporine A (CsA) in the prevention of IRI has been shown in different organs of several animal species but not clearly evaluated in lungs. Our objective was to evaluate the effects of CsA in ex vivo reperfused pig lungs.

Methods: 10 lungs were perfused with an extracorporeal perfusion circuit, and mechanically ventilated. CsA was administered before and during reperfusion procedure (either at 1 or 30µM).

Results: Lungs treated by 30 µM of CsA had increased capillary pressure (Pcap), pulmonary vascular resistances (PVR), lung permeability to proteins, IL1 beta and TNF alpha concentrations in bronchoalveolar lavage (BAL). 1µM of CsA seemed to have no effect compared to control group.

Lungs parameters

<table>
<thead>
<tr>
<th>Pcap (mmHg)</th>
<th>PVR total (mmHg/V.min)</th>
<th>K (min^-1)</th>
<th>[IL1] in BAL (TNFα) in BAL (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=12)</td>
<td>6.72±1.20</td>
<td>9.54±0.62</td>
<td>0.006±0.004</td>
</tr>
<tr>
<td>CsA 1µM (n=6)</td>
<td>8.00±1.19</td>
<td>13.08±4.99</td>
<td>0.012±0.010</td>
</tr>
<tr>
<td>CsA 30µM (n=13)</td>
<td>13.73±3.93</td>
<td>16.02±1.53</td>
<td>0.024±0.009</td>
</tr>
</tbody>
</table>

*: p<0.05 between control and CsA 30µM; K: coefficient of permeability to Dextran of the capillary-alveolar membrane.

Discussion: CsA, at the concentration of 30 µM, seems to be deleterious in lung IRI. The hemodynamic effects of CsA may explain these results.

222 Comparison between SCOT-15® and Perfadex® as lung preservation solutions

Anne Olland 1, Caroline Meers 1, Malika Benahmed 1, Karima Elbeyad 1, Shana Wauters 1, Eric Verbeeken 1, Geert Verleden 1, Izie Namer 1, Dirk Van Raemdonck 1, 1 Laboratory for Experimental Thoracic Surgery, KU Leuven, Leuven, Belgium; 2 Laboratory for Biophysics and Nuclear Imaging, HU Strasbourg, Strasbourg, France; 3 Laboratory for Morphologic and Molecular Pathology, KU Leuven, Leuven, Belgium; 4 Laboratory for Pneumology, KU Leuven, Leuven, Belgium

Objectives: SCOT-15® is a low K+ solution including polyethyleneglycol (PEG) as a colloid for protection of endothelium. PEG was demonstrated to have immuno-camouflage properties and has been tested for kidney, pancreas and liver preservation. This study compares the properties of SCOT-15® for lung preservation with Perfadex® as a golden standard.

Methods: Two groups of 6 pigs each were compared. After 2L cold pulmonary plegia with either Perfadex® [P] or SCOT-15® [S], lungs were stored cold for 4 hours. Peripheral lung biopsies were taken for High Resolution Magic Angle Spin (HRMAS) detection of colloids. Lung function was assessed in an ex vivo lung perfusion and ventilation model. Pulmonary artery flow and pressure were recorded for pulmonary vascular resistance (PVR), mean airway pressure (mAWP) for lung compliance and blood gases on the perfusion outflow line for partial oxygen pressure (P02). Wet-to-dry weight ratio (W/D) was recorded for Dextran of the capillary-alveolar membrane.

Results: PVR was significantly lower in [S] compared to [P] (p=0.04). There were no differences in mAWP (p=0.13), mPaw (p=0.24) and W/D (p=0.06). HRMAS spectra showed presence of PEG in peripheral lung tissue in [S].
Conclusion: Lungs preserved with SCOT-15® had lower vascular resistance with comparable oxygen capacity reflecting well preserved endothelial function. Experiments with longer cold ischemia are needed to assess the relevance of this solution.

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MSK1 kinase in obliterative bronchiolitis following heterotopic tracheal transplantation

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2Laboratoire d’Innovation Thérapeutique, Université de Strasbourg - UMR 7200, Illkirch, France

Introduction: Obliterative bronchiolitis (OB) occurs during chronic allograft rejection of lung transplantation. OB is characterized by airway epithelium degradation, and obstruction of the small airways with inflammatory infiltrate and fibrosis. MSK1 is a nuclear kinase that activates NFκB in inflammation. Our hypothesis proposes MSK1 as an actor in OB via NFκB-induced activation of pro-inflammatory genes like IL-6.

Methods: In the mouse model of heterotopic tracheal transplantation, tracheal MSK1 and IL-6 mRNA levels were quantified by qPCR. Mice were treated i.p. with compound H89, a MSK1 inhibitor (10mg/kg/day) or solvent (DMSO 5%). Tracheal sections were stained with hematoxylin-eosin, and epithelium degradation measured. CD3+ cells (SP7 anti-CD3 mAb, Abcam) were counted and dendritic cells (DC, H2-I-A/I-E mAb, M5/114) labeled on fresh tracheas.

Results: MSK1 and IL-6 mRNA levels were increased in allografts by 68% ± 8% and 86% ± 2%, respectively, at D7 as compared to D0 and unmodified in isografts. Progressive epithelium degradation reached 77±4% of the total epithelium at D3 and was inhibited upon H89 treatment of 44±10% (p<0.05). In isografts, epithelium degradation also occurred (18±10%). CD3+ cell recruitment reached 208±82 cells/mm² at D7 and was inhibited to 16±8 cells/mm² (p<0.05), compared to isografts (17±9 cells/mm², NS). DC recruitment also occurred in allografts (525±73 cells/mm² at D3 and 1065±368 at D7) as compared to D0 (290±17). No effect of H89 was observed on DC recruitment at D3. Inflammatory luminal infiltrate was inhibited at D7 by 44±15%.

Conclusion: Inhibiting MSK1 is therefore a potential strategy to help combat obstruction after lung transplantation in this OB model.

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Development of a novel model of obliterative bronchiolitis following orthotopic lung transplantation in the rat

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Emanuele Cozzi1, Federico Rea3, Fiorella Calabrese1, 
1Laboratory of Pulmonology, Catholic University Leuven, Leuven, Belgium; 2Pathology, Catholic University Leuven, Leuven, Belgium; 3Laboratory of Thoracic Surgery, University Hospitals Zurich, Zurich, Switzerland

Background: Long-term survival after lung transplantation (LTx) is hampered by Bronchiolitis Obliterans Syndrome (BOS), morphologically presented by OB. Since the pathogenesis is still not fully understood and the prognosis remains poor a good animal model is indispensable.

Aims: The development of a new model of BOS after LTx.

Methods: C57B16 mice underwent LTx with BALB/c donor lungs and were sacrificed at 2, 4, 6, 10 and 12 weeks after LTx. Staining with H&E and Sirius Red (not shown) were performed.

Results: Histology showed two types of lesions. Type I lesions are characterized by lymphoctic bronchiolitis and functional lung parenchyma. These lesions seem to resolve over time. Type II lesions are demonstrated by fibrotic plugs growing into the airway lumen, resembling true BO lesions in humans. The surrounding parenchyma however is not functional.

Conclusions: Allograft LTx in mice mimics human histology of BO, optimisation of this model will open new perspectives to study pathogenesis of chronic rejection after LTx.

49. Are needles really enough?

P226

Late-breaking abstract: Do trainee respiratory doctors under supervision achieve acceptable results with EBUS-TBNA?

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Background: Endo-bronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is a useful tool in the staging and diagnosis of thoracic malignancy. There is limited evidence on the safety and efficacy of instructing respiratory trainee doctors in EBUS-TBNA.

Aims: To compare the results obtained by trainee respiratory doctors performing EBUS-TBNA as principal operator supervised by consultant respiratory physicians, to the results obtained from consultants as principal operators. We aim to discover if trainees can perform this procedure with acceptable accuracy and safety.

Methods: All EBUS reports were retrospectively collected between February 2009 and July 2010. The reports were analysed to determine the sensitivity, specificity and diagnostic accuracy for the EBUS operator, and rates compared for trainees, consultants and published series. Complication rates were also compared.
Results: Overall sensitivity and diagnostic accuracy were similar for trainees as primary operator compared to consultants. There were no significant adverse events in either group (table1).

Table 1. Sensitivity, specificity and diagnostic accuracy of EBUS-TBNA

<table>
<thead>
<tr>
<th>Operator</th>
<th>Total Positive</th>
<th>False</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trainee</td>
<td>21</td>
<td>2</td>
<td>0.93</td>
<td>87.5</td>
<td>100</td>
</tr>
<tr>
<td>Consultant</td>
<td>77</td>
<td>18</td>
<td>0.6</td>
<td>89.8</td>
<td>100</td>
</tr>
</tbody>
</table>

Conclusion: Provided there is close supervision by a consultant, trainee respiratory doctors performing EBUS-TBNA as primary operators appear to have similar safety and efficacy results.

P227 Late-breaking abstract: Radial probe endobronchial ultrasound scanning assessing invasion depth of central lesions in the tracheobronchial wall

Jing Li, Ping-ping Chen, Yu Huang, Zheng-xian Chen. Respiratory, Guangdong Academy of Medical Science, Guangdong General Hospital, Guangzhou, Guangdong, China

Background: Patients with central tracheobronchial benign or malignant lesions who have not received surgical treatment can be treated by interventional techniques. The accuracy of the invasion depth of central lesion in tracheobronchial wall plays an important role in making interventional treatment plan. This study used radial probe endobronchial ultrasound (EBUS) scanning to evaluate the accuracy of the invasion depth of central tracheobronchial lesions, and the influence of EBUS scanning in treatment plan making and guidance.

Methods: A radial ultrasound probe with a balloon sheath was introduced through the channel of a flexible bronchoscope. The balloon at the tip of the probe was inflated with distilled water until coupling with the airway wall under endoscopic control. The image of EBUS, which revealed the layered structure of the tracheobronchial wall, could be achieved.

Results: Total of 125 patients were enrolled in the study. 30 patients underwent surgical operation and pathologically proved the EBUS diagnosis accuracy of 90% (27/30), sensitivity and specificity were 88.9% (24/27) and 100 (3/3) respectively. In response to EBUS images, 40 approaches were altered or guided: lymph node metastasis and compressive lesions was diagnosed by EBUS-guided transbronchial needle aspiration (n=8); Lesions ablation with laser or electricity were stopped when EBUS demonstrated close range with vessels or perforation possibility (n=3), stents size were changed (n=4), operation was canceled (n=3) and foreign body was removed (n=2).

Conclusions: EBUS can be a useful tool in assessing the central lesion invasion to the tracheobronchial wall.

P228 A comparison of the combined ultrasound of the mediastinum by use of a single EBUS scope versus two scopes EBUS and EUS for lung cancer staging

– A prospective study

Amar Szuhajowski1, Paweł Koczko2, Jerzy Soja3, Piotr Talar2, Wiesław Czajkowski1, Łucyna Rudnicka-Sosin4, Adam Cmiele5, Jerzy Wojciech Czajkowski2, Lucyna Rudnicka-Sosin4, Adam Cmiele5

1Endoscopy Unit, Pulmonary Hospital, Zakopane, Poland; 2Dept. of Medicine, Jagiellonian University, Krakow, Poland; 3Dept. of Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland; 4Dept. of Pathology, Pulmonary Hospital, Zakopane, Poland

Introduction: The aim of the prospective trial was to compare diagnostic yield of the combined ultrasound of the mediastinum for lung cancer (LC) staging by use of a single EBUS bronchoscope – (CUS) and two scopes: EBUS and ultrasound gastrointestinal (EUS) – (CUS).

Methods: In consecutive LC patients in stage IA-IIIB the CUS or CUSb were performed under mild sedation in consecutive LC patients (pts) with enlarged or normal mediastinal nodes on CT scans. All non-small cell LC pts with negative CUS-NA underwent subsequently the transcervical extended bilateral mediastinal lymphadenectomy (TEMLA) as a confirmatory test and if negative underwent systematic lymph node dissection (SLND) by thoracotomy.

Results: From Jan. 2008 to Dec. 2010 in 588 LC pts who underwent CUS-NA there were 1529 mediastinal nodes biopsied (EBUS-NA – 805, EUS-NA – 724). The CUS-NA revealed metastases in 273/588 pts (46.4%) and a prevalence was 52.3%. In 272 CUS-NA negative pts and in 5 pts suspected for metastases, who underwent subsequent TEMLA and SLND metastatic nodes were diagnosed in 35 pts (5.9%), in whom double or multilevel N2 disease was found in 14 of them (2.4%). A diagnostic sensitivity, specificity, accuracy, PPV and NPV of CUS-NA were 88.6%, 98.4%, 92.7%, 98.25% and 88.6%, respectively. In pts with nodes highly suspected for metastases by echosonography positive results were obtained by both methods in 96.7% and in all small cell LC pts. The results of EUS-NA of 675 supraretral (M1-staging) impacted patients were performed under general anesthesia in 24 pts (4.1%). The CUS-NA influenced on T staging in 38 pts (6.5%).

No severe complications of CUS-NA were observed.

Conclusions: The CUS-NA is especially effective for mediastinal N staging but it also plays an additional role for TM staging in LC patients.

P230 Complication rate of EUS-NA and EBUS-TBNA in mediastinal nodal aspiration: A meta-analysis

Ardia van Breda, Bob von Bartheld, Jouke Aannema. Department of Pulmonology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands

Introduction: Echopneal and endobronchial ultrasound-guided fine needle aspiration (EUS-NA/EBUS-TBNA) are rapidly spreading minimally-invasive techniques for the diagnosis and staging of lung cancer and sarcoidosis. Generally, endosonographic procedures are considered to be safe although several severe complications have been reported in case reports. We performed a meta-analysis to assess the morbidity of EUS and EBUS for mediastinal nodal analysis.

Methods: A PubMed and Embase search was performed including all original studies (1999 - October 2010) using EUS and EBUS for mediastinal nodal analysis. Case-reports and studies not mentioning procedure morbidity were excluded from analysis.

Results: 353 studies (118 EUS, 74 EBUS, 10 both) were reviewed of which 151 were excluded form analysis. The other 202 studies consisted of 17200 patients (EUS: 7504 patients, EBUS: 8742, both 954). In those patients, 72 complications (0.42%) were reported of which 36 severe (0.21%) (pneumothorax, n=9; thoracic bleeding, n=5; esophageal rupture, n=5; mediastinitis, n=4) and 36 minor (0.21%) (minor pain, n=10; sore throat, n=9; hemoptysis, n=4; fever, n=2). Of the severe complications 20 occurred at EUS (0.27%) and 12 at EBUS (0.14%). No procedure-related deaths were reported.

Conclusions: The morbidity of mediastinal nodal endosonography is low and mortality has not been reported. The complication rate might well be underestimated due to underreporting, publication and performer bias. Further prospective evaluation is warranted to determine the actual complication rate of endosonography and identify possible subsets of patients that are at risk for complications.

P231 Is there a role of EBUS in the decision-making of endoscopic treatment for carcinoid tumor?

Korkut Bostanci, Jose Rojas-Solano, Heinrich D. Becker. Department of Interdisciplinary Endoscopy, Thoraxklinik at Heidelberg University, Heidelberg, Germany

Determination of the depth of invasion of carcinoid tumors is the most important finding for choosing the appropriate mode of therapy, whether it be local laser destruction or surgical resection, yet at present, endosonography and bronchoscopy have not been very adequate for the decision. We assessed the usefulness of endobronchial ultrasonosonography (EBUS) in the determination of the depth of tumor invasion of the tracheobronchial wall in carcinoid tumors.

From 2005 to 2010, 18 patients with carcinoid tumors were evaluated with this high resolution computed tomography (HRCT), bronchoscopy and EBUS prior to surgery. EBUS by a 20MHz-radial probe with balloon was performed in all cases to determine the size of the tumor, the depth of invasion, and to evaluate the relationship between the size of the tumor, the depth of invasion and EBUS.
of the tumor with the adjacent vessels and lymph nodes. All patients were operated on in days after bronchoscopy. Histopathological findings were compared with the HRCT, bronchoscopy and EBUS findings.

The tumor was visualized with EBUS in all cases. The exact size of the tumor could be measured in 15 cases, while in 3 cases it was out of range of EBUS. When compared to the pathological size EBUS measurements were more accurate than HRCT measurements. In 3 cases with no lesion but just atelectasis in HRCT, EBUS revealed only superficial infiltration of the bronchial wall with the tumor and the cartilage was intact, indicating a tumor potentially suitable for bronchoscopic resection. In all patients, surgery confirmed EBUS findings.

Our study showed that EBUS evaluation in carcinoma tumors adds to bronchoscopic and radiologic findings and can be useful in decision making for local laser destruction instead of surgical resection.

P232
Endosonography for the diagnosis of lymphoma
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Introduction: Transesophageal and transbronchial ultrasound-guided fine needle aspiration (EUS-FNA/EBUS-TBNA) are well-established procedures for mediastinal nodal staging of patients with non-small cell lung cancer (NSCLC). Malignant lymphoma often presents with intrathoracic lymph node enlargement. Data on the role of EUS-FNA and EBUS-TBNA for the diagnosis of mediastinal lymphoma are limited.

Objective: To assess the role of endosonography (EUS-FNA/EBUS-TBNA) for diagnosing mediastinal lymphoma.

Methods: We retrospectively analyzed 30 patients with suspected (recurrent) lymphoma in which mediastinal lymph nodes were investigated by endosonography using 22-Gauche needles. All patients had a final diagnosis of lymphoma (Hodgkin/Non-Hodgkin lymphoma), based on either surgical procedures, endosonography or clinical follow-up.

Results: We found that sensitivity, specificity and positive predictive value were 46%, 88% and 26% respectively. No complications occurred.

Conclusion: EUS-FNA and EBUS-TBNA have moderate sensitivity in diagnosing mediastinal malignant lymphoma. Therefore, negative test results should be followed by surgical or clinical staging procedures. Future studies should concentrate on a more detailed analysis of cell specific markers on cytology samples (eg flow cytometry) and the use of histology needles.

P233
The impact of rapid on site evaluation of cytological specimens on a new endobronchial ultrasound (EBUS) service
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Background: Mediastinal lymph node sampling using endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) has been shown to have a rapid role in the staging and diagnosis of lung cancer. It may also have a role in the diagnosis of benign diseases (e.g. sarcoidosis). For many experienced bronchoscopists EBUS-TBNA is a new technique with a steep learning curve. We introduced an EBUS service at our institution in January 2010. Whenever possible we undertook the procedure with a consultant cytopathologist who allowed rapid on site evaluation (ROSE) of specimens and real time feedback on specimen quality.

Aims: To assess the impact of ROSE in a newly established EBUS service.

Methods: We reviewed the impact of ROSE on the procedure duration, amount of lidocaine local anaesthetic (ILLA), amount of intravenous sedation (midazolam and alfentanil) and the diagnostic procedure rate in our first 30 EBUS cases.

Results: ROSE of cytological specimens was available for 22 (73.3%) of our first 30 cases. The availability of ROSE resulted in a significantly shorter procedure time (39.7 (SD ± 3.8) minutes Vs 57.3 (± 4.4) minutes, p = 0.01), and significantly lower amounts of sedation with midazolam (5.8 ± 2.2 mg Vs 9.0 (± 2.4 mg, p=0.002) and alfentanil (522.7 ± 187.5) μg Vs 781.3 (± 311.6) μg, p=0.01).

There was no difference in the amount of LLA or in the percentage of cases in which diagnostic material was obtained (82.8% with ROSE and 87.5% without ROSE).

Conclusions: ROSE of TBNA samples results in a significant reduction in length of procedure and the amount of sedation required for EBUS. The provision of ROSE is an important consideration in the development of an EBUS service.

P234
Outcomes of non-diagnostic endobronchial ultrasound guided tranbronchial needle aspiration
Thumalaunghe Thangakanum1, Bernard Yung1, Johnsson Samuel1, Gazin Bostanci2, Kanwar Pannu1, Dipak Mukherjee1. 1Respiratory Medicine, Basildon University Hospital, Basildon, Essex, United Kingdom; 2Department of Histopathology, Basildon University Hospital, Basildon, Essex, United Kingdom.

Introduction: Endobronchial ultrasound-guided tranbronchial needle aspiration (EBUS-TBNA) is a diagnostic procedure for the evaluation of mediastinal lymph nodes and masses. Although it has been proved to be a helpful diagnostic procedure for mediastinal node metastasis, the value of negative EBUS is not clear.

Methods: Retrospective review of the EBUS procedures. Results: A total of 106 EBUS procedures were attempted over 18 months, 105 procedures were completed. 1 patient did not co-operate and the procedure was abandoned. All the procedures were done with local anaesthesia and conscious sedation. In 4, EBUS did not show any significantly enlarged lymph nodes, so no samples were taken. The mean age of the patients was 65.6 yrs (range 22-87 years), with 68 males (64.2%). In 97 of 101 lessons sampled (97%), EBUS-TBNA yielded representative samples. In 51 cases the EBUS sample yielded diagnosis and were considered true positive. In the rest 50 cases the samples were non-diagnostic, of which 19 were true negative based on either mediastinoscopy or follow up. Four were false negative. The remaining 27 need follow up to know whether they are true negative or otherwise. In the 74 cases the overall sensitivity, specificity, positive predictive value and negative predictive value were 92.7%, 100%, 100% and 32.6% respectively.

Conclusions: EBUS-TBNA yielded diagnosis in half of the cases. In majority of patients with non-diagnostic EBUS, based on multi-disciplinary team review it was decided to follow up rather than directly proceed with mediastinoscopy or surgery because of either high risk for surgery or low clinical probability of malignancy.

P235
Endobronchial ultrasound-guided tranbronchial needle aspiration in the diagnosis and staging of lung cancer
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Objective: The aim of the study was to assess the diagnostic yield of the real-time endobronchial ultrasound-guided tranbronchial needle aspiration (EBUS-TBNA) in the diagnosis and staging of lung cancer.

Patients and methods: 134 patients with suspected lung cancer with mediastinal and/or hilar lymph nodes underwent EBUS-TBNA using the convex probe EBUS. All patients with negative EBUS-TBNA subsequently underwent the surgery or mediastinoscopy as a confirmatory test.

Results: One hundred thirty four patients underwent CP-EBUS-TBNA between December 2007 to December 2009. There were 233 mediastinal & hilar lymph nodes biopsied (stations: 2R-34R-73. 4L-21, 7-65, 10R-23, 10L-5, 11R-26, 11L-17). EBUS-TBNA revealed metastatic lymph node involvement in 54 of 134 patients (40.3%) and in 56 of 233 biopsies (24%). In 80 patients with negative or uncertain EBUS-TBNA who underwent subsequent surgery, mediastinoscopy, mediastinal nodes were diagnosed in four patients (3%) in stations: (4R-2-4L-1 J 7-1). The false-negative results of biopsies were found only in small nodes < 1cm. A diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of EBUS-TBNA was 93.1%, 100%, 90%, 94.5%, and 96.9%, respectively there was no significant relation between lymph node location and EBUS-TBNA cytology results. No complications of EBUS-TBNA were observed.

Conclusion: EBUS-TBNA is an effective and safe technique for diagnosis & mediastinal staging in patients with lung cancer. In patients with negative results of EBUS-TBNA, surgical exploration of the mediastinum should be performed.

P236
Endobronchial ultrasound for the diagnosis of granulomatous disease
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The aim of this study was to evaluate the yield of EBUS-TBNA in the diagnosis of granulomatous lymph nodes.

Patients and methods: All patients, from October 2005 to October 2010 in Hospital U Germans Trias I Pujol (Badalona) and Hospital U La Fe (Valencia), with hilar or mediastinal granulomatous lymph nodes were collected. Diagnosis of sarcoidosis was established based on clinical and radiological findings, supported by histologic evidence of noncaseating epitheloid-cell granulomas in the absence of necrosis or organism. Diagnosis of tuberculosis (TB) was made by the presence
of necrotizing granulomas with exclusion of other granulomatous or cultivation of Mycobacterium tuberculosis (MTB).

**Results:** 34 patients were diagnosed: 15 sarcoidosis, 16 TB, 1 silicosis, 1 tuberculosis-like, and 1 with HIV infection and reconstitution of immune response syndrome with granulomatous lymphadenitis. Sarcoidosis patients had a average age of 49 years, 9 males, and had sarcoidosis and everyone had mediastinal and hilar lymphadenopathies and 5 showed lung nodules. 36 lymph node stations were explored (average 2.4) and was punctured station 7 (15 times) and 10 L (6). EBUS-TBNA was decisive in 10 cases. TB mean age of was 49 years, 12 males and 2 HIV. 8 had prior suspicion of TB, 6 with PPD skin test + and 6 showed also lung injuries. 44 lymph nodes stations were explored (average 2.8), the more punctured was stations 7 (14 times) and 4R (10). Necrosis was found in 9 cases and in 6 in culture of MTB was positive and EBUS-TBNA was decisive in 9 cases. There were no complications of the technique.

**Conclusion:** EBUS-TBNA is a safe and cost effective diagnostic method that was decisive in involvement with granulomatous disease.

**Introduction:** The learning curve required for the EBUS-TBNA diagnostic procedure in patients with mediastinal or hilar lymph nodes from different aetiologies is still unclear. No evidence is available regarding the procedure’s influence on the parameters, such as length of procedures or the number of lymph node passes required for obtaining the diagnosis.

**Methods:** The learning curves of two experienced bronchoscopists who conducted exhaustive theoretical training on EBUS and 10 supervised procedures were prospectively analysed. The number of suitable samples and accuracy were assessed in six groups of 20 consecutive patients with >10 mm lymph nodes on chest CT or > 3 mm if positive increase in uptake on PET. The number, location, and size of punctured lymph nodes, the passes made in each node, and the length of the procedure were also recorded.

**Results:** Over 13 months, 215 lymph nodes in 120 patients were evaluated by EBUS-TBNA. The number of adequate samples and accuracy were 90.5% and 85.4% respectively (lymph nodes as the unit of analysis) and 89.2% and 84.9% respectively (patient as unit of analysis). A significant increase was observed, approaching 90% after the first 60 procedures. The mean number of passes in each lymph node was 2.1 (standard deviation 0.7), lymph nodes examined per patient 1.8 (0.8), and length of procedure 30 (8.5) minutes.

**Conclusions:** Experienced bronchoscopists need to perform more than 60 procedures to achieve acceptable diagnostic yield. Learning allows improvement in the quality of the samples obtained and the number of lymph nodes studied per patient.

**EBUS-TBNA learning curve for mediastinal and hilar lymph node diagnosis**

**Introduction:** EBUS-TBNA is a safe and cost effective diagnostic method that was decisive in involvement with granulomatous disease.

**Methods:** The learning curves of two experienced bronchoscopists who conducted exhaustive theoretical training on EBUS and 10 supervised procedures were prospectively analysed. The number of suitable samples and accuracy were assessed in six groups of 20 consecutive patients with >10 mm lymph nodes on chest CT or > 3 mm if positive increase in uptake on PET. The number, location, and size of punctured lymph nodes, the passes made in each node, and the length of the procedure were also recorded.

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**Conclusions:** Experienced bronchoscopists need to perform more than 60 procedures to achieve acceptable diagnostic yield. Learning allows improvement in the quality of the samples obtained and the number of lymph nodes studied per patient.

**P238**

EGFR direct sequencing on TBNA samples

Pierdonato Bruno, Maria Cristina Esposito, Giorgia Osman, Federica Fioretti, Giorgia Gencarelli, Alberto Ricci, Salvatore Mariotta.

**Results:** EGFR mutation detected in cytological samples of lymph nodes from patients with NSCLC. EGFR mutation detected in 2 cases (12,5%). In 3 cases, EGFR mutation was not detected in cytological samples.

**Conclusions:** EGFR mutation detected in cytological samples by lymph nodal TBNA: Our study supports the use of EGFR mutation detection in lymph nodes of patients with advanced NSCLC. The combination of EGFR mutation detection and histology can provide valuable information for the treatment of these patients.

**Introduction:** EGFR mutation detection in cytological samples of lymph nodes from patients with NSCLC is of great importance for the selection of targeted therapies. EGFR mutation detection by direct sequencing of exons 19 and 21 of EGFR gene can be performed also on TBNA cytological samples with the same reliability offered by the histological samples obtained from the same patient.

**P239**

EGFR mutation detected in cytological samples by lymph nodal TBNA: Our first year experience

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**Introduction:** EGFR mutation detection in cytological samples by lymph nodal TBNA: Our first year experience.

**Methods:** We evaluated the yield and applicability of molecular testing for EGFR status (S) in TNBAs cyto specimens during the first year practice for each of two brs. We had retrospectively analyzed the results of 60 patients (ps) and 72 lymph nodal (LN) TBNA We used ROSE (Rapid on site examination) to recognize lymphocytes (LC) in the slide as a prove that the material was LN. We did at least 3 aspirations in LN >12 mm in long axis in LC setting. We considered a successful puncture one with LPC in cyco exam evaluated by pathologist. We found 4 ADC female cases with light or no smoking habit and we asked to our lab to evaluate the slides for EGFR S.

**Results:** We found No DNA to be amplified 1 case, 2 cases Wild type EGFR and 1 with M 19 exon.

**Patients EGFR status in our series**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>EGFR status</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.F. n°1</td>
<td>76</td>
<td>Wild type</td>
<td>IV</td>
</tr>
<tr>
<td>D.S. n°2</td>
<td>78</td>
<td>Wild type</td>
<td>IV</td>
</tr>
<tr>
<td>C.M. n°3</td>
<td>67</td>
<td>Exon 19</td>
<td>IIB</td>
</tr>
<tr>
<td>C.M. n°4</td>
<td>65</td>
<td>Unknown</td>
<td>IV</td>
</tr>
</tbody>
</table>

All cases are female with adenocarcinoma.

**Conclusion:** Our study demonstrates the feasibility and applicability of molecular testing for EGFR status in lymph nodal TBNA. EGFR mutation detection in lymph nodal TBNA can provide valuable information for the selection of targeted therapies. The combination of EGFR mutation detection and histology can provide valuable information for the selection of targeted therapies. EGFR mutation detection in lymph nodal TBNA can provide valuable information for the selection of targeted therapies.

**P240**

A prospective study of TBNA of 63 patients from a tertiary care hospital in India

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**Introduction:** Role of TBNA (Transbronchial Needle Aspiration) through bronchoscopy in diagnosing mediastinal and hilar lesions is well established. Unfortunately, it is underutilized due to poor training and wide variation (20 to 89%) in yield. The yield is dependent on operator’s expertise besides size and location of the lesion. We share our experience of a prospective study of 63 cases performed at a tertiary care hospital by single operator over 6 months.

**Method:** Bronchoscopy was performed in 63 consecutive patients with mediastinal and hilar lesions. Besides TBNA, bronchial biopsy, BAL and trans-bronchial lung biopsy were also performed when needed.

**Results:** Most frequent presenting complaint was fever 63% (n=38) with or without cough. Lymph nodes greater than 0.5cm in size were punctured. Subcarinal node (n=62) and right paratracheal node (n=42) were most commonly punctured. TBNA was performed with 21 G needle and piggyback method was found to be most effective method for puncture. A positive result was obtained in 84% of patients (n=53). Tuberculosis was diagnosed in 55% (n=29) of the positive cases, malignancy in 23% (n=12) and sarcoidosis in 21% (n=11). Fungal infection and carcinoma were also seen.

**Conclusion:** In expert hands, yield of TBNA can be quite high (84% in this study) and even small nodes can be targeted. In India, the cost of EBUS procedure is $600 vs. conventional TBNA, which costs $200 and is available in very few centers. Authors recommend, especially for developing countries, that before proclaiming EBUS as the new gold standard, proper method of conventional TBNA should be learned, which is more cost effective. Patient should be referred for EBUS only when TBNA is inconclusive.

**P241**

Role of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of bronchogenic carcinoma

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Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a technique used for the diagnosis of peribronchial/peritracheal mass lesion and the staging of bronchogenic carcinoma.

The aim of this study is to determine the role of EBUS-TBNA in patients with bronchogenic carcinoma.
with peribronchial/peritracheal mass without endobronchial lesion suspected for bronchogenic carcinoma and patients with a diameter of mediastinal/hilar lymphadenopathy bigger than 1 cm in CT, prediagnosed as bronchogenic carcinoma. Between April 2010 and January 2011, 56 patients with mean age 60.8 years (47 M/9 F) were admitted to study. EBUS-TBNA was performed to only lymph node in 47 patients, both lymph node and mass in 5 patients and only mass 4 patients. The definite diagnosis was done in twenty five patients without endobronchial lesion. Ninety six out of ninety seven lymph node aspiration was positive (70% mediastinal/22 hilar). One patient diagnosed with mediastinoscopy. (Sensitivity 98.9%, specificity 100%, PPV 100%, NPV 67% and accuracy 98.9%).

Twelve N3 lymph node were positive for malignancy. Seven out of nine mass biopsy were diagnosed as malignant. Two patients were diagnosed with other diagnostic procedures. No complication was observed during EBUS-TBNA.

In conclusion, EBUS-TBNA seemed a safe and effective technique in making bronchogenic carcinoma diagnosis for mediastinal/hilar lymph nodes and intrapulmonary masses.

P242
TBNA (submucosal) for diagnosis of mesothelioma (and ROSE for a faster one)
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We describe a malignant pleural mesothelioma (MPM) case diagnosis obtained with submucosal (SM) TBNA (transbronchial needle aspiration) and ROSE (Rapid on site examination). A 64 year old man was admitted to our unit because of pneumonia and scanty pleural effusion (PE) on chest radiography (see figure, Thorax CT scan).

To our knowledge, this is the first time that a mediastinal involvement of MPM is approached via TBNA and ROSE was diagnostic for Epithelial MPM.

P243
Transbronchial needle aspiration (TBNA) in the diagnosis and staging of lung cancer in a large cohort of patients
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Introduction: TBNA is a minimally invasive bronchoscopical technique, that allows to examine mediastinal and hilar lymph nodes, avoiding surgical mediastinal exploration.

Objectives: The aim of this study was to assess the sensitivity and diagnostic accuracy of TBNA in a large cohort of patients. In addition, we apprased the relationships between TBNA yield and lymph node size and location.

Methods: Between March 2009 and November 2011, we prospectively examined 110 patients (age range: 30 to 87 yr, 51 F) with suspected lung cancer and enlarged mediastinal lymph nodes. Each patient performed TBNA during flexible bronchoscopy with rapid-on-site evaluation.

Results: TBNA was positive in 88 of 110 patients with suspected lung cancer (80%). No complications was observed. The lymph node size cut-off point, that better identified patients with positive aspirate was ≥ 24 mm (0.83 sensitivity and 0.51 specificity; AUC=0.861, p=0.018 by ROC curve analysis).

In all patients, the subcarinal and anteromedian carina lymph node locations had the higher percentage and the left paratracheal lymph node location had the lower percentage of patients with positive aspirates (96%, 75% and 50%, respectively).

Conclusions: Our results confirm that in a large cohort of patients conventional TBNA is a sensitive technique and an effective tool to diagnose and stage lung cancer and show that ≥ 24 mm lymph node size has a high likelihood to be associated to a positive aspirate. Additionally, the lymph node location may play a role in the diagnostic yield of TBNA.

50. COPD management
P244
Adherence of stable COPD patients to inhaled pharmacotherapy
Silvia Dumitru, Konstantinos Velentzas, Elpida Theodorakopoulou, Maria Harikiopoulou, Martha Andritsou, Alexia Chroniaou, Zafeiris Sardelis, Elias Kamin, Panagiotis Demertzis, Epaminondas Korvam. 3rd Department of Pulmonary Medicine, Chest Diseases Hospital “Sotira”, Athens, Greece

Since compliance to inhaled medications is related to a decreased risk of hospitalizations and death in COPD, we aimed to investigate the compliance of COPD patients to inhaled pharmacotherapy. We studied 208 COPD patients [age 63±8 years; 77 in stage II (37%); 112 in stage III (54%) and 19 in stage IV (9%)]. Non-compliance was defined as the incorrect use of the inhaler device, as a sporadic or pen use due to perception of no effect or due to wrong information, when patient or his caregiver declares non-compliance, and when medication is not prescribed regularly. Results are reported for Tiotropium (T), fixed combinations of either Salmeterol/Fluticasone (SF) or Formoterol/Floventine (FF), and Salmeterol (S) or Formoterol (F) as single agents. Overall compliance to the above inhaled agents was 92%, 84%, 81%, 75% and 68% respectively. According to GOLD staging, compliance to T was 87% (II); 94% (III); 95% (IV); to SF 78% (II)-84% (III)-92% (IV); to FF 78% (II)-79% (III)-100% (IV); to SF 87% (II)-100% (III) and to FF 61% (II)-86% (III). Major reasons for non-compliance to SF were the incorrect technique to inhale from the Diskus (78%), to FF the perception of no effect when inhaling from the Turbohaler (50%), while reasons for non-compliance to T were the incorrect technique of using Handihaler (36%), no purchase or prescription renewal (36%) and sporadic use (28%). We conclude that compliance rates were higher for Tiotropium and the fixed combination of Salmeterol/Fluticasone. There was an increasing compliance in relation to COPD severity, while the detected reasons of poor compliance should be tackled through a more effective contact between COPD patients and their physicians.

P245
Health-related quality of life (HRQL) and patient-reported outcomes (PRO) in COPD patients receiving add-on therapy with EPs® 7630
Heinrich Mattheiss1, Dina Pliskevich1, Thorsten Reinecke1, Fatih-Abdul Malek3, 1Medical Director Emeritus, Department of Pneumology, University Hospital Freiburg, Freiburg i. Br, Germany; 2Faculty of Internal Medicine No. 4, National O. O. Bogomolets Medical University, Kiev, Ukraine; 3Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

HRQL and PRO are important measures for treatment evaluation and assessment of health condition. In an RCT (ISRCTN06187133) in patients with COPD stage II/III, add-on ther-
Japy with EPs® 7630, a herbal drug preparation from Pelargonium sidoides roots (Umckaloabo®; ISO Azneumittel, Ettlingen, GBR), significantly prolonged time to exacerbations and reduced their frequency. We also investigated HRQL and further PRO parameters assessed during the trial. Patients with a standardised COPD baseline treatment according to GOLD were randomly allocated to a double-blind 24-week oral add-on therapy with 30 drops EPs® 7630 (n=99) or placebo (n=101) thrice daily. HRQL/PRO were assessed by St. George’s Respiratory Questionnaire (SGRQ), EQ-5D, Integrative Medicine Patient Satisfaction Scale (IMPSS), Integrative Medicine Outcomes Scale (IMOS), patient-reported intensity score of cough, sputum production and sternal pain while coughing, and drug tolerability. After 24 weeks, patients treated with EPs® 7630 reported a significantly more improved HRQL compared to placebo (SGRQ total score, p<0.001; EQ-5D VAS, p<0.001). For EPs® 7630, patient satisfaction with treatment was significantly improved compared to placebo (SGRQ total score, p<0.001; EQ-5D VAS, p<0.001). For EPs® 7630, patient satisfaction with treatment was significantly improved compared to placebo (SGRQ total score, p<0.001; EQ-5D VAS, p<0.001).
higher (IMPS, $p<0.001$), patient-reported treatment outcome significantly better (IMOS, $p<0.001$) and the mean intensity score during exacerbations significantly lower ($p<0.024$). Incidence of adverse events was comparably low in both groups.

**Conclusion:** Add-on therapy with EPs$^4$, 7630 led to a statistically significant and clinically relevant improvement of HRQL and other PRO (total score difference of SGRQ = 4 points) including good long-term tolerability in patients with COPD stage II and III.

P246

**Treatment with megestrol acetate and testosterone increases body weight and muscle mass in COPD cachexia**

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Underweight COPD patients with involuntary weight loss have a poor prognosis; no effective therapy is available. We conducted the first clinical trial determining whether combined therapy with an appetite stimulant and an anabolic steroid would have beneficial body composition effects.

We conducted a 12 week pilot study in which 4 men and 5 women (age 64±10y, FEV1%pred 31.9, BMI 18.3±3) with low testosterone (T) levels (average 490ng/dl in men and 12ng/dl in women) and weight loss >10lb over the previous year received 800mg megestrol acetate/day plus weekly testosterone enanthate injections.

Two women and two men had COPD exacerbations and did not complete the study. On treatment, T levels were 334 (79.9, 95.0) 1.05 (0.97, 1.14) 0.75 (0.68, 0.83) 0.91 (0.83, 1.0).

Rate per patient per year (95% CI)

Mean (SEM) pre-BD FEV1 (L)

Baseline

Former smokers Current smokers

ROF (n=1700) PBO (n=1740) ROF (n=1164) PBO (n=1173)

Mean age, yrs (SD)

66.46 (8.94) 66.39 (8.80) 60.83 (8.80) 60.71 (8.29)

Mean rate of moderate or severe exacerbations per patient per year

0.86 (0.79, 0.95) 1.03 (0.97, 1.14) 0.75 (0.68, 0.83) 0.91 (0.83, 1.0)

Frequency of patients with moderate or severe exacerbations (%)

Baseline

52 wks

52 wks

Impact of roflumilast treatment on the rate and duration of exacerbations and overall steroid load in patients with COPD

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Background/Rationale: Roflumilast (ROF), an oral, selective phosphodiesterase 4 inhibitor, reduces the rate of moderate and severe exacerbations. Oral steroids are frequently used to treat exacerbations, but whether ROF affects oral steroid exposure is not known. Using data pooled from two 1-year studies (NCT00297102 and NCT00297115), we investigated the effect of ROF on the need for oral steroids.

Methods: Patients with COPD and a history of exacerbations and chronic bronchitis were randomised to receive ROF 500µg once daily (n=1537) or placebo (PBO; n=1554) for 52 weeks. Rate of moderate or severe exacerbations was a co-primary endpoint. Steroid use (dose/day and days of use) for the treatment of exacerbations was recorded.

Results: The mean rate of moderate or severe exacerbations in ROF- and PBO-treated patients (per patient/year) was 1.14 vs 1.57, respectively (reduction 16.9%; p<0.0005). The mean number of days on which patients had exacerbations was reduced with ROF vs PBO (moderate 23.7 vs 27.3; severe 21.5 vs 25.0). The mean duration (days) of exacerbations was also reduced with ROF vs PBO (moderate 13.4 vs 13.9; severe 17.4 vs 19.5). Patients receiving ROF had a lower mean daily steroid dose (3.9mg/day) than those receiving PBO (4.2mg/day).

Conclusions: In patients with COPD associated with chronic bronchitis, ROF significantly reduced the rate of moderate or severe exacerbations. ROF treatment also reduced the duration of exacerbations, particularly for severe exacerbations requiring hospitalisation. The overall steroid load and duration of steroid treatment needed to manage exacerbations was lower with ROF.

P247

**Efficacy of roflumilast in former and current smokers with COPD**

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We conducted parallel-group randomized controlled multicentre trials involving 68 COPD patients. The participants were randomly assigned to real (RA, n=34) or placebo acupuncture (PA, n=34). Both group received real or placebo needling once a week for a total of 12 weeks. We evaluated not only change in functional outcomes but also by nutritional status, exercise capacity and severity of dyspnea.

In the 5 subjects who completed, DEXA revealed 2.0±1.1kg lean mass and 2.5±2.0kg fat mass increase (both $p<0.05$). No adverse treatment effects were detected.

Combination therapy reversed involuntary weight loss and increased muscle mass in cachectic COPD patients. Though the interventions were apparently well tolerated, subject dropout rate was high. Larger randomized long-term studies with functional outcomes are needed.

P248

**Acupuncture improves nutritional status and BODE index in patients with chronic obstructive pulmonary disease: A randomized, placebo-controlled trial**

Masa Suzuki1,2,3, Motonari Fukui2, Tetsuhiko Shiota4, Kazuo Endo5, Susumu Saito3, Kenkazu Aihara4, Masatake Matsumoto6, Shinko Suzuki1, Ryo Iitaka1, Manabu Ishitoko1, Masaya Takeamura1, Yoshikazu Haru1, Hiroshi Kagio1, Masatake Hirabayashi1, Shigero Muro1, Michiaki Mishima1, 1Dept of Respiratory Medicine, Graduate School of Medicine Kyoto University, Kyoto, Japan; 2Dept of Respiratory Medicine, Kitano Hospital Medical Research Institute, Osaka, Japan; 3Dept of Respiratory Medicine, Ako City Hospital, Hyogo, Japan; 4Dept of Respiratory Medicine, Hyogo Prefectural Amagasaki Hospital, Hyogo, Japan; 5Dept of Clinical Acupuncture and Moxibustion, Meiji University of Integrative Medicine, Kyoto, Japan

Introduction: Prognosis of COPD patients is influenced not only by pulmonary functions but also by nutritional status, exercise capacity and severity of dyspnea. Our previous study (Suzuki M et al. ARCCM 2010; 181: A5420) showed that acupuncture improved significantly not only Modified Borg Scale at the end of 6-minute walk test (MBS), but also various general conditions of COPD patients including quality of life (SGRQ).

Aim and Objective: To determine whether acupuncture had any effects on nutritional status and BODE index of COPD patients in our previous study.

Methods: We conducted parallel-group randomized controlled multicentre trials involving 68 COPD patients. The participants were randomly assigned to real (RA, n=34) or placebo acupuncture (PA, n=34). Both group received real or placebo needling once a week for a total of 12 weeks. We evaluated not only change in

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Former smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>66.46 (8.94)</td>
<td>66.39 (8.80)</td>
</tr>
<tr>
<td>Mean rate of moderate or severe exacerbations per patient per year (95% CI)</td>
<td>0.86 (0.79, 0.95)</td>
<td>1.03 (0.97, 1.14)</td>
</tr>
<tr>
<td>Mean (SEM) pre-BD FEV1 (L)</td>
<td>Baseline</td>
<td>0.97 (0.01)</td>
</tr>
<tr>
<td></td>
<td>52 wks</td>
<td>1.06 (0.01)</td>
</tr>
<tr>
<td></td>
<td>Mean (SEM) post-BD FEV1 (L)</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>52 wks</td>
<td>1.17 (0.01)</td>
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</table>

**Abstract P247 – Table 1**

<table>
<thead>
<tr>
<th></th>
<th>ROF (n=1700)</th>
<th>PBO (n=1740)</th>
<th>ROF (n=1164)</th>
<th>PBO (n=1173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>66.46 (8.94)</td>
<td>66.39 (8.80)</td>
<td>60.83 (8.80)</td>
<td>60.71 (8.29)</td>
</tr>
<tr>
<td>Mean rate of moderate or severe exacerbations per patient per year (95% CI)</td>
<td>0.86 (0.79, 0.95)</td>
<td>1.03 (0.97, 1.14)</td>
<td>0.75 (0.68, 0.83)</td>
<td>0.91 (0.83, 1.0)</td>
</tr>
<tr>
<td>Frequency of patients with moderate or severe exacerbations (%)</td>
<td>Baseline</td>
<td>0.97 (0.01)</td>
<td>1.05 (0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52 wks</td>
<td>1.06 (0.01)</td>
<td>1.00 (0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SEM) post-BD FEV1 (L)</td>
<td>Baseline</td>
<td>1.08 (0.01)</td>
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</tr>
<tr>
<td></td>
<td>52 wks</td>
<td>1.17 (0.01)</td>
<td>1.11 (0.01)</td>
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</tbody>
</table>
P250

Time to desaturation under 1 minute on the 6m walking test predicts chronic domiciliary oxygen therapy in COPD patients

Luisa Eiroa, Ruth Piti, Juan Manuel Palmero, Juan Marco Figuera, Ana Isabel Velázquez, Magdalena Alonso, Jesús Rodríguez, Canelaria Ramos, Irene De Lorenzo, José Luis Trujillo, Alfonso Tauromi, Ignacio García Talavera, Pau Blanca. Pulmonology Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Canarias, Spain

Introduction: Time to desaturation (T90) on the 6 minute walking test (WT6m) and time of these patients.

Objective: To analyze the gasometric parameters changes on copd patients with early desaturation on the WT6m 5 years later.

Material and Methods: We studied 83 patients with COPD and desaturation on WT6m under 1 minute. 73 men/10 women, average 60.9 years old, FEV1: 42% pred and PO2 66mmHg. We did spirometries, gasometries, WT6m every 6 months for 5 years. The patients who during the study needed domiciliary oxygen therapy, were prescribed by their phvicians who did not know the content of the study.

Results: After 5 years, 65% of patients without early desaturation (T90 under 1 minute) had chronic domiciliary oxygen therapy vs 11% of patients with desaturation after 1 minute (T90 > 1 min), p< 0.01.

Conclusions: Moderate-severe COPD patients desaturating before 1 min on the WT6m need oxygen therapy before 5 years opposed to patients with desaturation after 1 minute. Early desaturators need more clinical and gasometric controls.

P251

Tiotropium vs salmeterol in GOLD II and maintenance-naïve COPD patients: Subgroup analyses of POET-COPD™ trial

Irene De Lorenzo, José Luis Trujillo, Alfonso Tauroni, Ignacio García Talavera, Pau Blanca. Pulmonology Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Canarias, Spain

Introduction: Tiotropium (18 μg qd) vs salmeterol (50 μg bid), in a) GOLD II and b) maintenance-naïve (not previously receiving maintenance therapy from GOLD stage II) disease. Inclusion criteria: COPD, smoking history ≥10 pk-yr, post-bronch forced expiratory volume in 1s (FEV1) ≤70% pred, FEV1/forced vital capacity (FVC) ≤0.7, history of ≥1 moderate or severe exacerbation in prior year. Primary endpoint: time to first exacerbation.

Results: Of 7376 patients randomized and treated, 3614 were GOLD II and 1343 maintenance naïve at randomization. GOLD II: 69.3% men, age 63.2 yrs, 37.3 pk-yr. maintenance naïve: 72.2% men, age 60.9 yrs, 34.6 pk-yr. Tiotropium prolonged time to first exacerbation in both GOLD II and maintenance-naïve groups: hazard ratio (95% confidence interval [CI]), tiotropium vs salmeterol: 0.88 (0.79-0.99), P=0.028 vs 0.79 (0.66-0.97), P=0.028. Exacerbation rates (per pt-yr), tiotropium vs salmeterol: GOLD II: 0.55 vs 0.60, rate ratio (RR) (95% CI) 0.91 (0.81-1.01), P=0.072; maintenance naïve, 0.38 vs 0.49, RR (95% CI) 0.77 (0.63-0.94), P<0.05.

Conclusions: Similar to overall cohort in POET-COPD™, tiotropium improved outcomes vs salmeterol in GOLD II and maintenance-naïve subgroups of COPD patients with an exacerbation history. Funded by Boehringer Ingelheim/Pfizer.

P252

Efficient deposition and absorption of orally inhaled indacaterol in the lungs

Ruth Lock1, Deandre Price2, Sanjeev Klimdi1, Ralph Weesner3, Markus Weiss2, Hisanori Hara4, Ilona Pylvänäinen5, Guenter Kaiser2. 1Translational Sciences, Novartis Institutes for Biomedical Research, Horsham, United Kingdom; 2Translational Sciences, Novartis Pharma AG, Basel, Switzerland; 3Integrated Information Sciences, Novartis Pharma AG, Basel, Switzerland

Introduction: Indacaterol (IND) is an inhaled long-acting β2-agonist for the once daily treatment of COPD, delivered via single-dose dry powdered inhaler (Onbrez® Breezhaler®). Study aims were 1) To determine absolute bioavailability (Fabs) of IND after oral inhalation compared with intravenous (IV) dosing and 2) To determine relative contributions of lung and gastrointestinal tract (GIT) absorption to systemic exposure of inhaled IND. To this end, inhaled IND was also administered concurrently with oral activated charcoal.

Methods: A two-part randomized, open label, single-dose study in healthy volunteers (HV). In Part 1, 8 HV received an IV infusion of 200 μg IND and an inhaled dose of 300 μg IND in a 2-way, 2-sequence crossover design. In period 3 all 8 HV received an inhaled dose of 600 μg IND together with an oral dose of charcoal. Treatments were separated by 7 days. In Part 2, VT3 was HV received oral doses of IND (600 μg) and charcoal. Blood samples were taken for PK analysis and IND was determined in serum by LC-MS/MS. PK parameters were determined by non-compartmental methods.

Results: The Fabs of inhaled IND was 45%. Oral activated charcoal was effective in blocking the oral absorption of IND. The relative bioavailability of inhaled IND with oral charcoal was 74% compared to inhalation without charcoal.

Conclusion: Almost 75% of the systemic exposure following inhalation of IND was due to lung absorption, and 25% was due to GIT absorption. Based on an Fabs of 45% for inhaled IND, the fraction of the inhaled dose deposited and absorbed in the lungs was estimated as 34% of the nominal IND dose, providing evidence of effective lung delivery of inhaled IND via Onbrez® Breezhaler®.

P253

Subclinical cardiac dysfunction in moderate to severe chronic obstructive pulmonary disease (COPD) patients

Alessia Verduri1, Barbara Bottazzari2, Chiara Leuzzi3, Roberto D’Amico1, Piera Boschetto1, Maria Grazia Modena1, Alberto Mantovani2, Leonardo M. Fabbri3, Bianca Beghi2. 1Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy; 2Research Laboratory Immunology & Inflammation, Clinical Institute Humanitas, IRCCS, Milan, Italy; 3Department of Cardiology, University of Modena and Reggio Emilia, Modena, Italy; 4Department of Clinical and Experimental Medicine, University of Ferrara, Ferrara, Italy

Introduction: COPD is associated with chronic cardiovascular (CV) comorbidities. IL-6 is a pro-inflammatory cytokine involved in COPD pathogenesis. In Part 2, PTX3 is an inflammatory marker that might have role in systemic inflammation associated with COPD and comorbidities.

Objective: To investigate the relationship between circulating IL6 and PTX3 and COPD, we assessed cardiac function in COPD patients clinically free of CV disease and association among IL6 and PTX3, COPD severity, right (RV) and left (LV) ventricular function.

Methods: In 70 COPD (GOLD diagnosis) outpatients, ≥10 pk-yr, ≥50 yrs, we assessed Charlson Comorbidity Index, BODE index and echocardiography. LV systolic dysfunction was defined as LV ejection fraction (EF) <40%. Triacipul Cardiac Magnetic Resonance Imaging (CMRI) and RV function are according to JASE guidelines 2010. IL6 and PTX3 levels were measured by sandwich enzyme-linked immunosorbent assay. Associations were assessed by a linear regression model.

Results: We analyzed 70 COPD pts (52 M), mean age 68 yrs, mean EF 45. COPD severity was GOLD I in 10 pts, II in 34, III in 26. Mean Charlson Index was 4 (range 2-8), mean BODE index 2.3, mean±SD DLC0x/VA 73±7.8, mean±SD LVEF 70±7. Mild RV diastolic dysfunction was found in 40/70 pts (57%). Interestingly, positive significant association (r=0.4, p=0.001) was found between TAPSE and DLC0x. Positive significant association (p=0.08,p=0.03) was also found between age and PTX3.

Conclusions: COPD pts with reduced DLC0x have reduction of TAPSE suggesting a subclinical RV systolic dysfunction. In this population, IL6 and PTX3 levels were not associated with cardiac dysfunction and COPD severity. By contrast, PTX3 is associated with aging.

P254

Effects of ambulatory oxygen on exercise capacity and vital parameters in patients with COPD

Baris Yilmaz, Enis Yentürk, Derya Yememtir, Firdavs Atabey, Esin Tuncay. 1Vehdali Chest Diseases and Surgery Hospital, Pulmonary Medicine, Istanbul, Turkey

Introduction: Ambulatory oxygen is defined as supplemental oxygen during exercise. Candidates for ambulatory oxygen are either already on long term oxygen therapy (LTOT) or show evidence of exercise desaturation.

Aim: The aim of this study is to evaluate the effects of ambulatory oxygen on exercise capacity and vital parameters in patients with COPD who didn't fulfill the criteria for LTOT.
Based Medical Decision Support, MMDS, Aalborg University, Aalborg, Denmark; Time required for PaO2 equilibration in patients with severe COPD

P257 Screening for malnutrition in outpatients with pulmonary diseases Siebring Schokker, J. Sebastiana Vroepeog, Luc H. Steenhuis, René Aalbers, Department of Pulmonary Diseases, Martini Hospital, Groningen, Netherlands

Background: Malnutrition has negative effects on patient outcome, in particular in patients with COPD. Recognition of malnutrition in an early phase might be beneficial for patients and screening for malnutrition in an outpatient setting might, therefore, be worthwhile. Aim: To determine the extent of malnutrition in outpatients with pulmonary diseases using different methods. Methods: All patients visiting our outpatient department of pulmonary diseases for the first time (period Oct. 2010 - Feb. 2011) were screened for malnutri-
tion. Different methods were used to screen for malnutrition: body mass index (BMI), Short Nutritional Assessment Questionnaire (SNAQ), and a fat free mass measurement (FFM; bio-impedance by Bodystat® 1500).

Results: Data of 121 outpatients (mean age 59, 49% male, 29% COPD) were analysed. Obesity (BMI > 30) was found in 26% of patients and underweight (BMI < 21 in COPD, and respectively <18.5 or < 20 in non-COPD, aged ≥65 or >65 yrs) was found in 7 patients. The SNAQ score detected 9 and 3 patients being severely or moderately malnourished. FFM revealed 17 patients (14%) with malnutrition. Combining SNAQ and BMI resulted in detection of 17 malnourished patients. However, different patients are detected (Table 1).

Table 1. Malnutrition. FFM vs. SNAQ + BMI

<table>
<thead>
<tr>
<th>BMI</th>
<th>SNAQ + BMI</th>
<th>FFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

A low FFM was found more often in patients with COPD (23%) and in females (21%).

Conclusion: This study revealed malnutrition in 6 to 14% of outpatients with pulmonary diseases. Measurement of BMI only seems to underestimate nutritional problems. The discrepancies in detecting different patients emphasize the need for determining a gold standard for defining and measuring malnutrition.

P258 Comparison of costs of community-acquired pneumonia (CAP) treatment at patients with and without bronchial obstruction Yury Mostovoy, Hanna Demchuk, Propediatric Department to Internal Medicine, Vinnitsya National Medical University, Vinnitsya, Ukraine

With purpose to estimate economical costs of treatment of CAP at the patients with and without bronchial obstruction and without it the comparison of therapeutic expenses of CAP at 33 inpatients against a background COPD (basic group – BG) and 33 patients without COPD control group – CG) was performed by case-control method. Patients were represented by age and gender (main age- 63±14 years, 54.3% male). Average duration of hospitalization was similar: BG 34.7±9.9 days, CG 33.7±9.7 days (p>0.05). Patients were represented by mean ± SD. Duration of antibiotic therapy was longer in BG than in CG (12±4 vs 8±1 days). Portion of expenses for antibiotics higher was in BG than in CG (51.5% vs 45.5%, p<0.01). Average costs of treatment for patient in BG was 1229.5±467.72 UAN, but for patient of CG – 789.5±32.43 US (p<0.001). Due to obstruction, severe respiratory failure, slower improving CAP symptoms in BG therapy of these patients was more intensive. Severe 30% from BG were needed change of initial antibiotic to alternative, but nobody from CG. Duration of antibiotic therapy was longer in BG than in CG (12±4 vs 8±1 days). Portion of expenses for antibiotics were higher in BG than CG (51.5% and 44.3% agreeably (p<0.05). Treatment of bronchial obstruction and respiratory failure caused increasing costs for BG at the mean 389.45±34.76 UAN. Costs of treatment of cardiovascular diseases were similar in the both group: 10% in BG and 9.7% in CG (p<0.01) from total sum. More severe CAP at patients with COPD requires more intensive treatment involving bigger therapeutic and diagnostic resources. It considerably increases costs of medical care for this group of patients.

P259 Comorbidities in stage IV COPD patients Vanda Areias1, Susana Carreira1, Marisa Ayreias1, Paula Pinta1, Cristina Bárbara1, 2Pneumology Service II, Hospital Pulido Valente - Centro Hospitalar Lisboa Norte, Lisboa, Portugal; 2Pneumology Service, Hospital de Faro, Faro, Portugal

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is associated with...
many comorbidities, however the prevalence of these diseases varies in different studies.

Aim: To determine the prevalence of various comorbidities in stage IV COPD patients (pts), followed in a respiratory outpatient clinic of an University Hospital.

Methods: A questionnaire was designed and applied to stage IV COPD pts in order to characterize the disease and its comorbidities. Data were supplemented by consensus clinical files.

Results: We included 89 pts (87% male), with a mean age of 68±9 years. 79% were ex-smokers. Mean FEV1 was 38% of predicted and all of them had chronic respiratory failure. Thirty-five pts (39%) were frequent exacerbators (≥2 exacerbations in the last year).

Thirty-seven pts (42%) had at least one admission because of their respiratory disease in the last year and 66 patients (74%) in the last 5 years. Most pts had at least one comorbidity (97%), with an average of 4 comorbidities by patient and a mean Charlson index of 2.

The most frequent comorbidities were cardiovascular diseases (70%), erectile dysfunction (6%), sleep apnea syndrome (43%), dyslipidemia (35%), cataracts (31%), gastroesophageal reflux (29%) and diabetes (20%).

Frequent exacerbators were associated with a 5-fold increase in the odds ratio of having a comorbidity.

Frequent exacerbators had more gastroesophageal reflux (p=0.006) and more admissions in the last year and in previous 5 years (p<0.001).

Conclusion: This study confirms the high prevalence and association of comorbidities in stage IV COPD pts and its influence on exacerbations and admissions, justifying the need of a complete and integrative treatment approach.

P260 Fenspiride as complementary anti-inflammatory agent in therapy of patients with chronic obstructive pulmonary disease.

Tetyana Pertseva, Olena Myronenko, Natalya Klimenko. Internal Medicine Department, Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine

The aim of our study was to study the efficacy of fenspiride (F) in the complex therapy of patients with chronic obstructive pulmonary disease (COPD).

Study population: COPD pts with I-II stages (n=20) were observed on an exent 6-month treatment period. Among them were 13 males (65%). Mild age 49±0,2;11,32 year, duration of COPD 13,03±4,76. 1st gr. (10 pts) – combined therapy with F (160 mg/day) and fentolateral/praprotam bronhode (F+) (200±80 mcg/day). 2nd gr. (10 pts) – monotherapy with F+

Methods: Spirometry and pneumotonometer were performed on days 1, 90 and 180 by means MasterScreen Body/Def [“Jager”, German]. Functional status was accessed by six-minute walk distance (6MWD) test and Borg dyspnea scale. The St. George Respiratory Questionnaire (SGRQ) data were determined before and after treatment period.

Results: Significant increase in all of the SGRQ domains in pts of 1st gr (p<0.01) was observed. Essential increase of the 6MWD test result has been established on (25,15±5,5) meters in the 1st gr. Perceived dyspnea severity and leg fatigue severity were reduced in 1st gr (p<0.05). Reduction of bronchial obstruction was less considerable and was comparable in both groups (p=0.04 & p=0.038).

We didn’t received significant increases in the respiratory muscle strength (p>0.05).

Conclusion: The study demonstrated greater efficacy of long-term complex therapy with fenspiride and fentolateral/praprotam bronhode compared with fentolateral/praprotam bronhode alone in patients with COPD. This combination regimen can be recommended for the reduction of inflammation and prevention of disease progression in COPD patients.

P261 What are the factors related to misdiagnosing of COPD?

Jean Bourbeau, Denis O'Donnell, Francois Maltais, Darcy Marciniuk, Jean Bourbeau1, Shawn Aaron5, Ken Chapman6, Robert Cowie, Andrea Benedetti1, Tanya Aaron6, Bernard Tanguy, Ziad Rida. Consultation des Maladies Respiratoires et Allergiques, CHU Félix Guay, Saint Denis, Réunion Island, Reunion

The factors for COPD misdiagnosed by physicians are not known.

Methods: This research was part of the Canadian Cohort Obstructive Lung Dis ease (CanCOLD). Subjects were recruited (population-based sampling) from 9 cities. Physician-diagnosed COPD was based on patient self-reported. COPD was confirmed by spirometry, i.e., post-BD FEV1/FVC <0.70.

Results: This analysis included 2132 subjects from 5 cities. Of 163 with physician-diagnosed COPD, 79 were confirmed to have COPD by spirometry while 84 didn’t have COPD. 333 had COPD confirmed by spirometry but were undiagnosed, 910 were at risk (ever smoker) and 726 were healthy (never smoker). Among those with physician-diagnosed COPD as compared to undiagnosed COPD, diagnosed subjects were more likely to be current smokers (36% vs 20%, p<0.0001), to have chronic bronchitis (32% vs 12%, p<0.0001), wheezing (64% vs 38%, p<0.0001), dyspnea >35 MRC (22% vs 9%, p<0.0001), diagnosis of asthma (47% vs 23%, p<0.0001), and lower health status. Similar characteristics were present for physician-diagnosed COPD whether or not the diagnosis was confirmed by spirometry. Predictors of physician-diagnosed COPD included current smoking (OR: 1.86, 95% CI: 1.09-3.18), chronic cough (2.04, 1.13-3.69), chronic bronchitis (2.70, 1.45-5.04), and reduced physical health “SF-12” (0.96, 0.96-0.99).

Conclusions: Misdiagnosis and underdiagnosis of COPD is common. Current smoking, respiratory symptoms and reduced health seems to trigger physican to make diagnosis of COPD. The absence of these factors may result in underdiag-nosis.

Funding: CIHR Rx&D Collaborative Research Program; and the Respiratory Health Network of the FRHQ.

P262 Sublingual allergen extract immunotherapy in a rush pattern to reach the maintenance faster.

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Introduction: Sublingual immunotherapy was tried on some patients to evoke some faster and affordable immunotherapy modality to make the patient achieve the maintenance pleats within a very short time. Conventional method of immunotherapy is administered with long durations; rush immunotherapy is super fast methodology in attaining the maintenance/boosting module, which requires hospitalization and other precautionary methods, and multiple allergens’ vaccines to be administered within a short span of time. But in this method, it was found that within 15-20 days the relief of the immunotherapy was reached.

Material & method: 186 patients out of which 48 with urticaria allergic and 138 with allergic Rhinitis & Bronchial Asthma were selected. The therapy consists of administration of four vials of allergics extracts, 1st vial: 1:2500, 2nd vial 1:2,50, 3rd vial 1:25, and 4th vial 1:10 din. The 1st & the 2nd concs were administered in daily 6 hourly schedules in a graphically rising manner. The patients had been given pre-medication. Blood examination and IgE & IgG level estimation were done before & after 8 weeks.

Results: Some of the patients showed local skin reactions which subsided without drugs and no systemic reaction was noted. There was substantial decrease in IgE & increased IgG level, significant & marked satisfactory relief was observed in the patients symptomsatology, thus the procedure was graded as a very fast & affordable & SAFE immunotherapy.

P263 Adherence to sublingual immunotherapy in patients allergic to mites

Bashir Omarjee, Bernard Tanguy, Ziad Rida. Consultation des Maladies Respiratoires et Allergiques, CHU Félix Guay, Saint Denis, Réunion Island, Reunion

Background: Adherence is essential for effective treatment. Specific allergen immunotherapy (SLIT) should be continued until the patient has had substantially reduced symptom free for 3 or 5 years. Sublingual immunotherapy (SLIT) is referred to improve adherence to SLIT. The aim of this study was to identify factors that may influence adherence to SLIT.

Methods: We evaluated 610 patients (15-45 years), 54.4% male, monosensitized to house dust mites with moderate persistent rhinitis and mild persistent asthma, submitted to SLIT in the last 5 years. We analysed factors related to non adherence to SLIT.

Results: 81 patients (13%) suspended SLIT based on different motives: For 28 patients (35%), main reason for discontinuation of SLIT is inability to take medication according to schedule; 21 patients (26%) withdrew in the first 4 months because of local side effects. 14 patients (17%) due to symptoms resolution: they began to show a 30% improvement of their symptoms compared to the basal score, because of local side effects. 14 patients (17%) due to symptoms resolution: they began to show a 30% improvement of their symptoms compared to the basal score, because of local side effects. 14 patients (17%) due to symptoms resolution: they began to show a 30% improvement of their symptoms compared to the basal score, because of local side effects. 14 patients (17%) due to symptoms resolution: they began to show a 30% improvement of their symptoms compared to the basal score, because of local side effects. 14 patients (17%) due to symptoms resolution: they began to show a 30% improvement of their symptoms compared to the basal score, because of local side effects.

Conclusions: The main cause of SLIT cessation was desertion, suggesting a need of a greater number of clinical appointments, at least during the first six months of treatment. Candidates to SLIT should be well selected to improve adherence to treatment. The ineffectiveness of SLIT could not be explained by non-adherence.

51. Allergen immunotherapy and anti-immunoglobulin E
P264 Maintenance schedule of subcutaneous allergen immunotherapy more efficacious than pre-seasonal
Ewa Szwedocka 1, Grzegorz Siergiejko 1, Piotr Rapiszko 1, Zenon Siergiejko 1
1 Pediatrics, Gastroenterology and Allergology Department, University Children’s Hospital, Bydgoszcz, Poland; 2 1st Department, Medical Institute of Medicine, Warsaw, Poland; 3 Respiratory System Diagnostics and Bronchoscopy Department, Medical University, Bydgoszcz, Poland

Pre-seasonal (PS) and maintenance (M) schedules of specific subcutaneous immuno-
therapy (SCIT) with allergoids are used to treat patients suffering from seasonal allergic rhinitis. Which of them is more profitable? The aim of the study was to compare an efficacy of two schedules of SCIT, PS vs. M.
Fifty seven patients included into the study randomly divided into two groups: PS group (n=28) and M group (n=29). Allergovit® (606 - grass pollen allergopharma, Germany) was chosen to treat them. SCIT lasted 3 years. Every year since 1st May-31st August diary cards were fulfilled. Intensity of symptoms (sneezing, nose itching, rhinorrhea, nasal obstruction, eyes itching, lacrimation, eyes reddening, cough and shortness of breath) and concomitant drug consumption were evaluated. Serum total and SlgE were evaluated before and after stopping SCIT. Intensity of a pollinosis was evaluated every year. Each individual from PS group was injected 30 times and obtained cumulative dose of 86662 IU/SBU, whereas the one from M group - 41injections and 172892 SBU. In 2006 the highest concentration of grass pollen in the air was 197/m3, in 2007 much higher – 475/m3, and in 2008 – 247/m3. The highest intensity of the symptoms in both group were registered in the first season of SCIT (2006). No significant differences between PS and M were found. The intensity of the symptoms decreased in successive years of SCIT, and in M group was more evident. After SCIT the concentration of IgE and SlgE decreased significantly.

Conclusions: Both schedules, PS and M of SCIT with allergoid vaccine are effective in pollinosis patients, but M is more profitable.

P265 Pollen asthma treatment: Comparative efficacy study
Iryna Sygaieva. State Center for Preventive and Clinic Medicine, Kyiv, Ukraine

Background: Airborne pollen has always been one of the most common triggers of asthma, so there is vital need in efficient specific hypoensibilisation.

Aims and objectives: Principal aim was to check efficacy of different combinations of inhaled corticosteroid/long-acting β2-agonist upheld by specific immunotherapy and/or montelukast.

Methods: In open-label, randomized, parallel group, one-year panel study were involved 468 patients with pollen asthma (moderate-to-severe airflow limitations, bronchitis symptoms, and a history of exacerbations). All participants had completed allergy examination ( prick skin test), immunologic, and functional assessments and stating their asthma status. Participants were randomized in three equal groups, 156 patients each. First group got specific immunotherapy, second - montelukast (Singular), and third – both treatments. Entire population received budesonide/formoterol (Symbicort Turbuhaler) as well.

Results: After 52-week treatment first group exhibited strong remission in 68% patients assigned, second group – in 61% patients, and third group – in 79% patients. These changes were statistically independent of patient’s age, sex, and smoking status (p>0.01).

Conclusions: Budesonide/formoterol in conjunction with allergen-specific immunotherapy and montelukast proved to be the most successful combination for curing pollen asthma.

P266 Omalizumab in asthmatics with IgE levels > 700 IU/ml
Diego Maselli, Joseph Diaz, Jay Peters.

P267 Effects of add-on omalizumab therapy on airway wall thickening in severe persistent asthma
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Background: Omalizumab has an important role in inhibiting the allergic inflammation, and it could possibly contribute to decreased airway remodeling in patients with asthma.

Aims and objectives: The aim of the study is to assess the effects of omalizumab on airway wall thickening using computed tomography (CT).

Methods: Twenty-eight patients with severe asthma were randomized to treat with conventional therapy with (n = 13) or without omalizumab (n = 15) for 16 weeks. Airway dimensions were assessed by CT, and wall area corrected for body surface area (WAVA/BSA), percentage wall area (WAW), wall thickness (Vw/BSA) at the right apical segmental bronchus were measured before and after treatment. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaire (AQLQ) were also measured.

Results: Treatment with omalizumab significantly decreased WAVA/BSA, WAW and Vw/BSA (p<0.01), whereas conventional therapy had no change. In the omalizumab group, there were significant decrease in the sputum eosinophils (p<0.01), and improved forced expiratory volume in 1s (FEV1), morning expira-
tory peak flow and the AQLQ score. The changes in FEV1% predicted and sputum eosinophils were significantly correlated with changes in WAVA (r=0.88, p<0.001), and n=072, p<0.01, respectively).

Conclusions: These findings suggest that omalizumab reduced wall thickness and airway inflammation.

P268 Decreasing dose protocol for omalizumab treatment in oral corticosteroid allergic asthma patients
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Purpose: To evaluate the viability of a protocol for the progressive decrease of omalizumab dose in allergic GINA step V asthma patients.

Methods: To enter the protocol, the patients had to be receiving treatment with oral corticosteroids for a minimum of one year, oral corticosteroid dose had to have reached its lowest level and spirometry had to be ≥ than at entry. Intervention: a) The omalizumab dose was reduced by half; b) If patients were clinically stable after 6 months, the dose was reduced by half again; c) If needed, oral corticos-
teroids boosters were administered; d) When repeated boosters were needed and/or spirometry worsened, omalizumab dose was increased to the previous figure until the patient stabilized.

Results: The protocol started in July 2006 until December 2010. Forty-five adult patients (31 female) were included; three females were lost during follow-up. The omalizumab dose was decreased in 12 patients (26.6%); it was stopped in three and has not been re-introduced after 4, 12 and 21 months. These patients had been treated for 45, 34 and 18 months respectively. Of the nine remaining patients, in six the dose was reduced and did not need to be re-increased; in three the omalizumab dose had to be increased to the initial dose at months 10, 15 and 32.

Conclusion: 1) A progressive decrease in the dose of omalizumab was feasible and safe in 26% of the patients. 2) A treatment-free window period is possible, and in one patient lasted up to 21 months.

P269 The APEX study: Retrospective review of oral corticosteroid use in omalizumab-treated severe allergic asthma patients in UK clinical practice
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Treatments that reduce oral corticosteroid (OCS) use can help reduce the burden of asthma. We retrospectively reviewed OCS-sparing in 136 omalizumab recipients (age ≥12 years) with severe persistent allergic asthma. The primary endpoint was to compare the difference in OCS quantity given during 12 months pre- and post-omalizumab initiation. Secondary endpoints included changes in lung function, asthma exacer-
bations and healthcare resource utilization and OCS use in patients on continuous OCS at baseline. Mean (±SD) total quantity of OCS prescribed per year decreased by 34% (p<0.001) between the 12 months pre- (5.5±4.21 mg) and post-omalizumab initiation (3.6±3.73 mg). During 12 months post-omalizumab initiation 87 patients (64%) stopped/reduced OCS use and 66 (49%) completely stopped. Mean per-
cent predicted FEV1 increased from 60.0±17.63% at baseline to 75.2±21.79% at Week 16 of omalizumab therapy (p=0.001). The number of asthma exacerbations...
Severe uncontrolled asthma is a contraindication against allergen-specific immunotherapy due to increased risks of side effects and asthma exacerbations. Omalizumab (Xolair®) has been shown to be an effective treatment for patients suffering from severe allergic asthma and to increased safety of allergen Specif-IgEImmunotherapy SIT. We describe 3 patients (males, 28, 31 and 42years) with severe asthma GINA III-IV and total IgE ranging from 181 to 680 IU/ml undergoing a combination of Omalizumab and house dust mite-SIT. House dust mite (HDM) allergy was confirmed by clinical history, positive skin prick tests, elevated specific serum IgE and positive conjunctival challenge tests. In all 3 patients Omalizumab was initiated according to manufacturer’s recommen-dation. After 3 months in all patients asthma improved requiring less inhaled drugs and an improved quality of life. The felt effect of HDM exposure was also reduced but still present. Thus we add an allergen-specific immunotherapy with HDM as the asthma situation was stable now. We opted for an ultra-high induction regimen with a total of 6 injections over 4 hours and a cumulative dose of 50000 IU. Patients were closely monitored. All patients tolerated the ultra-high induction very well. The maintenance regimen of the HDM extract was then injected on a monthly base. Also Omalizumab was continued on the initial dose. Omalizumab may enable induction of allergen-specific immunotherapy with HDM in severe asthma patients otherwise not accessible to this approach. The long term efect of this combined treatment will have to be further evaluated to judge clinical and pharmacoeconomical aspects.

Biological monitoring of cellular effects of omalizumab with basophil degranulation test (BAT) in severe asthma

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The use of anti-IgE antibodies (Omalizumab) for the treatment of severe asthma is the first approach with biological drugs in this setting. IgE bound to receptor on responsive cells induce both mast cell and basophil degranulation with release of new mediators responsible of clinical features. There aren’t objective tests to demonstrate the biological effects to this treatment. We evaluated basophil degranu-lation during treatment with Omalizumab using a basophil degranulation test based on a one-step method of basophil staining after exposure to a specific allergen with flow cytometry that shows basophilic reactivity in vitro and their degranulation after coming in contact with specific allergens. This method is based on recognition of positive blood cells positive to marking with monoclonal antibody CD123 that together with citoaphilometric caratheristic by Forward and Side Scatter and the contem-porary negativity of expression of superficial antigen HLA-DR identify basophil granocyte subset. In these cells after specific stimulation in vitro, is possible to identify IgE degranulation for the expression on the citoplasmatic surface of the antigen with monoclonal antibody CD63.

Seven patients were examined with the test baseline and after 12 and 24 months of OMA treatment. After 24 months of treatment degranulated basophil cells were 0.7% in comparison 53.9% at 12 months and 53.5% at baseline and this decrease was associated both to clinical improvements and reduction in oral corticosteroid daily dosage. Basophil degranulation test may be an appropriate method to evaluate Omalizumab biologic therapy in severe asthma where response and treatment duration are important aims.

The APEX study: A retrospective review of responses of severe allergic asthma patients to omalizumab on continuous or non-continuous oral corticosteroids in UK clinical practice

Robert Levy-Naon1 on behalf of the APEX Study Investigators, Amr Radwan2, 1North West Lung Centre, Wythenshawe Hospital, Manchester, United Kingdom; 2Clinical Development & Medical Affairs, Novartis Pharmaceuticals UK Limited, Frimley/Camberley, Surrey, United Kingdom

Omalizumab is an effective add-on option for patients with severe allergic asthma (who remain uncontrolled despite inhaled corticosteroid therapy), many of whom are receiving oral corticosteroids (OCS). We retrospectively reviewed records from 12 months pre- and post-omalizumab initiation in patients (age ≥12 years) with severe persistent allergic asthma who were or were not receiving continuous OCS. Percentages of patients reducing/stopping OCS use, changes in exacerbation rates, hospitalization and accident/emergency visit rates, overall responder rates and FEV1 all improved post-omalizumab (table). Responses were similar when comparing those who were and those who were not on continuous OCS at baseline. In conclusion, the benefits of omalizumab in patients not receiving continuous OCS at baseline were at least as good as those in patients receiving continuous OCS at baseline.

The use of omalizumab is recommended for patients with severe persistent allergic asthma (IgE-mediated asthma): Pooled data from 3 UK centres

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Omalizumab is approved as add-on therapy for patients (age ≥6 years, European Union) with uncontrolled severe persistent allergic (IgE-mediated) asthma. Few studies have reported on omalizumab’s effectiveness on real-life outcomes in UK clinical settings. We report clinical outcomes in severe allergic asthma patients receiving omalizumab (150-600 mg q4wk or q2wk) at 3 UK centres (St Peter’s Hospital, Chertsey, Bradford Royal Infirmary, Colchester Hospital). Data were compared for 2-years pre-omalizumab and for the most recent assessment following omalizumab initiation. Patients (n=52; age 18–74 years) received omalizumab for an average of 982 days (range: 112–3839). 86.4% patients responded to treatment at 16 weeks. Following omalizumab, hospital admissions/bed days, A&E and GP visits decreased compared with pre-omalizumab (Table). Oral corticosteroid (OCS) use was also reduced post-omalizumab; mean maintenance dose of OCS pre- and post-omalizumab was 12.6 and 5.7 mg/day (n=45). Overall, mean [SD] improvement in AQLQ score was +1.39 [1.80] Asthma control also improved post-omalizumab, as shown by an overall increase in mean [SD] ACT of +7.29 [4.64]. Patients not receiving OCS at baseline (n=14) achieved higher mean [SD] AQLQ scores compared with those on OCS at baseline (n=29); 2.29 [1.23] vs 1.36 [1.77].

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REAL-LIFE EFFECTIVENESS OF OMAZUMAB IN PATIENTS WITH SEVERE ALLERGIC ASTHMA: POOLED DATA FROM 3 UK CENTRES

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Landmark study: A retrospective review of responses of severe allergic asthma patients to omalizumab on continuous or non-continuous oral corticosteroids in the UK clinical practice

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Omalizumab is an effective add-on option for patients with severe allergic asthma (who remain uncontrolled despite inhaled corticosteroid therapy), many of whom are receiving oral corticosteroids (OCS). We retrospectively reviewed records from 12 months pre- and post-omalizumab initiation in patients (age ≥12 years) with severe persistent allergic asthma who were or were not receiving continuous OCS. Percentages of patients reducing/stopping OCS use, changes in exacerbation rates, hospitalization and accident/emergency visit rates, overall responder rates and FEV1 all improved post-omalizumab (table). Responses were similar when comparing those who were and those who were not on continuous OCS at baseline. In conclusion, the benefits of omalizumab in patients not receiving continuous OCS at baseline were at least as good as those in patients receiving continuous OCS at baseline.
Long-term treatment with monoclonal antibodies anti-IgE in severe asthma: Follow-up of ten patients

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Omalizumab is a monoclonal anti-IgE antibody suggested for the treatment of very severe asthma. Duration of therapy remains an open question.

We tried to evaluate the long-term response to omalizumab in a population of patients who extended the treatment beyond the 12 months period suggested by EMEA, with the aim of contributing to establish the ideal duration of the therapy.

10 patients (8 females, 2 males, mean age:45 yrs), with severe allergic asthma, uncontrolled despite GINA Step 4 therapy, received optimized asthma therapy and omalizumab up to 36 months. They underwent complete clinical evaluation, spirometry tests and Asthma Control Test questionnaire every month.

Patients showed, after 24 months of treatment, persistence of good clinical and functional status. Omalizumab ACT score was reduced from a 9,9% improvement compared to basal value, FEV1 and MMFE showed an increase of 21% and 26%, with best values registered after 18 months. No side-effects were reported.

Long-term therapy with omalizumab in our patients was well tolerated with significant improvement of both symptoms and functional status. Our data suggest that omalizumab could be a good therapy for patients with severe asthma who do not respond satisfactorily to other therapies.

Omalizumab is a recombinant anti-IgE antibody with proven efficacy in severe allergic asthma. Little is known about immunological changes after decreasing or withdrawing of the therapy.

In the present study T lymphocyte cytokine profiles and frequency of regulatory T-cells before and during omalizumab therapy in patients with severe allergic asthma were examined.

Twenty patients with severe allergic asthma (14 female) who met the criteria for omalizumab therapy were treated for 12 months and after 16 weeks of therapy peripheral blood mononuclear cells were isolated and activated with anti-CD3/anti-CD28 antibodies. Cells were processed for intracellular cytokine staining and frequency of CD3+CD4+ interleukin (IL)-4, IL-5, IL-17 and IFN-γ positive cells was assessed. The frequency of CD4+CD25+FOXP3+CD127- regulatory T-cells was assessed.

Anti-IgE treatment did not lead to a significant change of intracellular IL-4, IL-5, IL-17, and IFN-γ in CD3+CD4+ T-cells. No differences in frequency of regulatory T-cells were found even after 16 weeks of therapy. Additionally, there was no significant change in frequency of regulatory T-cells (mean at baseline:Treg 11±6%, 50±5% interindividual variation in week+16 Treg 11±6%, 45±4%).

In this study there was no significant difference of the tested intracellular cytokines before and after anti-IgE therapy. Frequency of regulatory T-cells did not change significantly 16 weeks after initiation of anti-IgE therapy.
Patient physical activity and its relation with exercise capacity in patients with early COPD.

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Objective: To investigate differences between patients with COPD who achieve or not the minimum physical activity recommended by the American College of Sports Medicine (ACSM) according to age.

Methods: Physical activity in daily life (DynaPort monitor and SenseWear armband), lung function, exercise capacity, body composition, quality of life (HRQL), dyspnea level in COPD patients. We assessed PA (SenseWear Armband) for 7 days (reported as the average PAmod) in 123 (ex-)smokers (49 with COPD; 33 GOLD I and 16 GOLD II) and 94 non-smokers. Exercise capacity was determined by VO2max and six minute walking distance (6MWD).

Results: Group characteristics are given in table 1. PA was significantly correlated (p<0.001) with 6MWD (r=0.37 and r=0.27 with PApeak and PAmod, respectively) and VO2max (r=0.39 and r=0.35 with PApeak and PAmod, respectively).Stepwise multiple regression analysis showed that PAmod is determined by age (R²=0.17), 6MWT (R²=0.09), season of PA assessment (1=summer/spring/autumn, R²=0.02) and diagnosis of COPD (R²=0.02; total R²=0.30). PAmod is determined by season (R²=0.12), age (R²=0.05), 6MWD (R²=0.04), gender (R²=0.02) and COPD (R²=0.02; total R²=0.25).

Conclusion: PA is reduced in patients with mild COPD. Age, season of PA assessment and 6MWD are predictors of PA.
Activity limitations in patients with chronic obstructive pulmonary disease

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Aim: Breathlessness causes limitations in activities of daily living (ADL) in COPD patients. The aims of the study were to determine most prevalent ADL limitations, and to analyze relationship between changes in occupational performance and dyspnea, respiratory and peripheral muscle strength, fatigue, and quality of life in COPD.

Materials and methods: Thirty-five COPD patients (FEV1 50.6 ± 19.0% predicted, BMI 28.8 ± 4.9 kg/m²) and 10-paired patients living with their families (4 male, 66 [61–71] years, FEV1 39 ± 30.1% predicted, BMI 22 [20–29] kg/m²) using a multiaxial accelerometer (MiniMed, McRoberts, the Netherlands) during 12 hours/day for two consecutive weekdays. Other measurements were: spirometry, respiratory and peripheral muscle force (maximal respiratory pressures [MIP and MEP] and quadriceps one-repetition maximum test [1RM]), respectively, and functional exercise capacity (6-minute walk test, GMWT).

Results: The two groups had similar GMWT, MIP, MEP and quadriceps 1RM. Time spent walking/day was 37 [31–47] min/day in patients living alone and 49 [43–56] min/day in patients living with their families (p=0.129). Moreover, patients living with their families tended to spend more time lying/day (143 [112–244] vs. 87 [48–177] min/day, p=0.093).

Conclusion: These preliminary results suggest that patients with COPD living alone are more active in daily life than patients with their families, despite presenting similar functional exercise capacity and muscle force. This might implicate in a different treatment approach in patients living alone or with family.

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Daily physical activity in patients with COPD living alone or not: Preliminary results

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Background: Although patients with chronic obstructive pulmonary disease (COPD) are known to be physically inactive, we hypothesized that those living alone are less inactive in daily life than patients living with family in order to maintain their functional needs.

Objective: To compare the physical activities in daily life between patients with COPD either living alone or with their families.

Methods: Physical activities in daily life were evaluated in 10 patients living alone (4 male, 64 [61–68] years, FEV1 39 [26–62]% predicted, BMI 23 [21–30] kg/m²) and 10-paired patients living with their families (4 male, 66 [61–71] years, FEV1, 41 [30–49]% predicted, BMI 22 [20–29] kg/m²) using a multiaxial accelerometer (MiniMed, McRoberts, the Netherlands) during 12 hours/day for two consecutive weekdays. Other measurements were: spirometry, respiratory and peripheral muscle force (maximal respiratory pressures [MIP and MEP] and quadriceps one-repetition maximum test [1RM], respectively) and functional exercise capacity (6-minute walk test, GMWT).

Results: The two groups had similar GMWT, MIP, MEP and quadriceps 1RM. Time spent walking/day was 37 [31–47] min/day in patients living alone and 49 [43–56] min/day in patients living with their families (p=0.129). Moreover, patients living with their families tended to spend more time lying/day (143 [112–244] vs. 87 [48–177] min/day, p=0.093).

Conclusion: These preliminary results suggest that patients with COPD living alone are more active in daily life than patients with their families, despite presenting similar functional exercise capacity and muscle force. This might implicate in a different treatment approach in patients living alone or with family.

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Short-term effects of using pedometers to increase daily physical activity in smokers

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Aim: To evaluate the differences in the quality of life (QoL) of patients with Chronic Obstructive Pulmonary Disease (COPD) living in different countries.

Methods: A cross-sectional and comparative study with 80 COPD outpatients of the Respiratory Service of public hospitals of Salamanca (Spain) and Fortaleza (Brazil) from September to December 2010. The sampling was selected by pairs depending on the severity (Global Initiative for Chronic Lung Disease criteria). Socio-demographic and spirometric data (American Thoracic Society criteria) were collected. The QoL was evaluated by the St George Respiratory Questionnaire (SGRQ), a self-administered short form with 38 items and 5 domains (Activity limitations, Breathing symptoms, Cough, Exercise limitation). The total SGRQ score is calculated by the sum of all items.

Results: The severity was 7.5% of mild, 30% of moderate, 47.5% of severe and 15% of very severe COPD. The mean age of Brazilian patients was 66.6 years (SD 8.0years) and the Spanish one was 69.1 years (SD 8.9years). There were significant differences in gender, civil status, monthly income, place of residence, being smoker and ex-smoker, the forced expiratory volume in 1s (FEV1) in both samples. There were also significant differences in all domains and the total SGRQ and in all WHOQOL-Bref domains except the Environment. Brazilian patients presented higher scores in the SGRQ (lower QoL) while Spanish patients had lower scores in the WHOQOL-Bref (worse QoL).
Cystic Fibrosis (CF) is a chronic respiratory disease with a multisystemic involve ment resulting in peripheral muscle fatigue. There are specific questions that assess physical activity fatigue in children. Children Sport Fatigue Questionnaire (CSFQ) and Short Fatigue Questionnaire (SFQ).

Methodology: To validate the Spanish version of both questionnaires in healthy sportive children and to measure the sensitivity of both tools on children with CF that follow regular physical activity.

Results: With children: age (12±2.6 years), BMI (19±2.7 kg/m²), Cronbach index showed good consistency, 0.86 to 0.78. CSFQ and SFQ and intraclass correlation coefficient showed: 0.85 and 0.83, CSFQ and SFQ, respectively. CF children: age (13±3.8 years), BMI (18±2.7 kg/m²). Significant correlations were obtained between CFQ-R and CSFQ: Physical 0.76, Body 0.66 and Role 0.85 for CFQ-R14+. Digestive 0.34 and Treatment 0.33 for CFQ-R Child. Correlations between CFQ-R and SFQ: Physical 0.53 and Role 0.54 for CFQ-R14+ and Treatment 0.40 for CFQ-R Child.

Conclusion: The CSFQ and SFQ questionnaires are valid and reliable for assessing the fatigue caused by physical activity and being suitable for use in CF children that follow regular physical activity such as pulmonary rehabilitation.

53. Tuberculin skin tests, interferon-gamma release assays and beyond

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The specificity of a new skin test – Diaskintest (recombinant protein CFP10-ESAT6) in patients with sarcoidosis and non-tuberculous pulmonary diseases

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Background: DIASKINTEST (DST) is a recombinant protein combination of CFP10-ESAT6 for intradermal injection and does not cause delayed-type hypersensitivity reactions in the BCG vaccinated. Objectives and methods: We have used DST intradermally in a dose of 0.2 mg in 0.1 ml in 179 patients aged 18-69 yrs; 62 patients with morphologically identified sarcoidosis, 11 active tuberculosis (TB) patients and 106 patients with other non-specific inflammatory lung diseases. In 72 hours we measured the diameter of induration and hyperemia in mm. Positive response is evaluated as an any size induration, negative - no induration and hyperemia

Results: Among sarcoidosis patients we saw no reaction to DST – the negative results were in all 62 cases, and specificity of DST in this group was 100% [95%CI 99.9%-100%]. In 106 patients with non-tuberculous inflammatory lung diseases we had 8 positive result (2 patients with asthma, 2 with nonspecific pneumonia, 2 with lung cancer, 2 with COPD); specificity of the method in this group was 92.5% [95%CI 87.4-97.5%]. 2 of 11 TB patients had negative response to DST (1 patient with TB and hepatitis C and 1 with TB and alcoholism), so sensitivity is 81.8% for TB cases [95%CI 58.9%-100%]. In our previous research we had similar results using IFN-γ release assay (IGRA) in response of blood cells to ESAT-6 ex vivo, but in the clinical practice we see that the IGRA is more laborious method.

Conclusion: DST has high specificity in sarcoidosis patients and in patients with other nonspecific inflammatory lung diseases. DST may be used as an additional test for the differential diagnosis with TB in unclear cases.

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DIASTEST as a screening method at the mass child health examination for tuberculosis in Russia

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The purpose of this study was to investigate the possibility of differential diagnosis of tuberculosis infection in children and teenagers in the medical practice, which possesses a high specificity owing to the use of secretory proteins ESAT-6 and CFP-10 and its easy test version will allow to enhance the efficiency of tuberculosis infection diagnosis, reduce unnecessary expenses and improve the overall epidemic situation on tuberculosis.

Methods: We conducted a prospective study including consecutive household contacts of patients with active TB between January 2010 and July 2011. All contacts below the age of 35 years of age were interviewed and screened by TST. If the TST was below 6mm, contacts were asked to return for a second TST six weeks later. TST conversion was defined as a TST of greater than 6mm or a 5mm increase of the initial TST. Interferon Gamma Receptor Assay (IGRA), (T-spot test) was performed on those that had TST conversion to evaluate the booster phenomenon.

Results: Of 899 adult and paediatric contacts screened who had an initial TST of less than 6 mm, 189 contacts did not attend for a second TST. A total of 406 had TST performed. 344 contacts attended and did not show TST conversion and were therefore discharged. 68 contacts underwent TST conversion of whom 43 had an IGRA. Out of 43 contacts, 6 had a positive IGRA, 7 out of 43 were indeterminate and 30 were negative. Indeterminate and negative IGRA results were more common in children than in adults.

Conclusion: A two stage approach of TST may cause a booster effect and therefore should be confirmed by IGRA.

Rationale: The role of two stage tuberculin skin test (TST) of persons who have had close contact with a case of smear-or culture positive pulmonary tuberculosis (TB) (PTB) is unclear. A booster phenomenon with TST may occur and therefore screening with TST in a two stage approach may not be ideal [1].

Methods: We conducted a prospective study including consecutive household contacts of patients with active PTB between January 2010 and July 2011. All contacts below the age of 35 years of age were interviewed and screened by TST. If the TST was below 6mm, contacts were asked to return for a second TST six weeks later. TST conversion was defined as a TST of greater than 6mm or a 5mm increase of the initial TST. Interferon Gamma Receptor Assay (IGRA), (T-spot test) was performed on those that had TST conversion to evaluate the booster phenomenon.

Results: Of 899 adult and paediatric contacts screened who had an initial TST of less than 6 mm, 189 contacts did not attend for a second TST. A total of 406 had TST performed. 344 contacts attended and did not show TST conversion and were therefore discharged. 68 contacts underwent TST conversion of whom 43 had an IGRA. Out of 43 contacts, 6 had a positive IGRA, 7 out of 43 were indeterminate and 30 were negative. Indeterminate and negative IGRA results were more common in children than in adults.

Conclusion: A two stage approach of TST may cause a booster effect and therefore should be confirmed by IGRA.

Reference:

Variables responsible for tuberculosis positivity of household contacts of sputum positive TB cases
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In high TB endemic countries such as India, chemoprophylaxis is routinely offered only to contacts below 6 years of age. The possibility however remains that the index case may have transmitted the infection to other family members before the diagnosis of the disease. We evaluated this in a group of Indian patients. We did a cross sectional study of household contacts of the sputum positive TB patients diagnosed from our center that had no other index case at home present in or out of the past. The contacts were tested for tuberculosis infection using 5 TU PPD (Purified Protein Derivative) immediately after the diagnosis of the index case. An induration of more than 10 mm was taken as a positive result. A total of 179 household contacts of 50 index cases were evaluated. 85/79 (47.48%) were tuberculosis positive. 62/73 (86.06%) contacts below 6 years of age were infected. 31/44 spouses (70.45%) were tuberculosis positive as against 39/87 (44.82%) first degree relatives and 15/48 (31.25%) second degree relatives. 61/112 (54.46%) contacts sharing same bedroom were infected as against 37 (35.82%) not sharing the bedroom. The prevalence of infection of contacts correlated with the grade of sputum positivity of the index case. The variables that did not show any statistically significant correlation were presence of lung cavity, hemoptysis, level and gender. This study suggests the need for offering chemoprophylaxis to the contacts sharing bedroom including spouses in addition to contact children below 6 years of age.

Tuberculosis skin test size and risk of tuberculosis: A 12-year follow-up of contacts of TB cases
Onofre Morán-Mendoza1, Mark FitzGerald2, Kevin Elwood2, David Patrick2.

Background: There are no long-term cohort studies assessing the risk of developing active TB according to the tuberculosis skin test size in contacts of TB cases who did not receive treatment for latent TB infection (LTBI) or were receiving immunosuppressive treatments.

Objective: To assess the risk of TB – according to the tuberculosis skin test (TST) size in contacts of active TB cases who did not receive LTBI treatment.

Methods: This is a population-based retrospective cohort study of contacts of active TB cases recorded in British Columbia, Canada. We estimated the up to 12-year risk of developing TB for infected and non-infected contacts, according to tuberculosis skin test size – using incidence rates. Contacts with HIV infection or with LTBI were excluded from the analysis.

Results: Among 26,542 contacts, 180 individuals developed TB (tuberculosis rate 678/100,000). Non-infected Household contacts (tuberculosis skin test size 0-4 mm) had a TB rate of 1.014/100,000, those with a TST of 5-9 mm a TB rate of 2.162/100,000; and those with 10-14 mm a rate of 4.478/100,000. Non-infected Close non-household contacts had a TB rate of 222/100,000; those with a TST of 5-9 mm a TB rate of 296/100,000 and those with 10-14 mm a rate of 1,821/100,000.

Non-infected Casual contacts had a TB rate of 83/100,000; those with a TST of 5-9 mm a TB rate of 204/100,000 and those with 10-14 mm a rate of 860/100,000.

Conclusions: The risk of TB increases with TST size in all contacts; especially with close contacts. TB risk is high for all household contacts, including those considered non-infected. The risk of TB in non-household contacts is significant only when the TST is ≥ 10 mm.

Comparative study of the usefulness of TST and three interferon-gamma release assays (IGRAs) for the differential diagnosis of pulmonary tuberculosis
Yoshifuro Kobashi, Masaki Abe, Keiji Moura, Yasushi Obase, Naoyuki Miyashita, Mikio Oka. Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan

Objective: We compared the usefulness of tuberculosis skin test (TST) and three interferon-gamma release assays (IGRAs) (QuantiFERON-TB Gold (QFT-2G), QuantiFERON-TB Gold In-tube (QFT-3G), T-SPOT.TB) as the supportive method of diagnosing pulmonary tuberculosis (TB).

Methods: The subjects were 70 patients who required the differentiation of pulmonary TB clinically. The final clinical diagnosis of pulmonary TB in 22 patients and non-pulmonary TB disease was established by clinical specimens.

Results: In 22 patients with pulmonary TB, the positive response rate was 60% on TST, 80% on QFT-2G, 85% on QFT-3G and 95% on T-SPOT.TB. In 48 patients with non-pulmonary TB disease, the positive response rate was 47% on TST, 9% on QFT-2G, 9% on QFT-3G, 13% on T-SPOT.TB. Indeterminate results on three IGRAs were recognized in one patient each on QFT-2G and QFT-3G among patients with pulmonary TB in three patients on QFT-2G and two patients on QFT-3G among patients with non-pulmonary TB disease. However, there were no indeterminate results on T-SPOT.TB in either patient group. Patients with false-negative or indeterminate results on IGRAs had severe underlying diseases or were receiving immunosuppressive treatments.

Conclusions: T-SPOT.TB provided the best positive response rate for patients with pulmonary TB among three IGRAs, although T-SPOT.TB may have problems in the specificity of diagnosing TB disease. Therefore, we think it is important to perform T-SPOT.TB in combination with QFT to elevate the sensitivity of the diagnosis of TB disease based on the findings in this study.
Aim: To assess the prevalence of LTBI in the risk groups: 1. homeless, 2. close contacts, 3. casual contacts, 4. nursing home pensioners, 5. random population subjects from Krakow (controls) by QFT-GIT and TST, to compare the agreement and kappa of these tests at 5, 10, 15 mm of TST cut-off and to establish the best TST cut-off for the diagnosis of LTBI.

Material and methods: From July 2007 to October 2009 QFT-GIT test was performed in 785 subjects: in group 1 (n = 150); 2 (n = 171); 3 (n = 163); 4 (n = 152); 5 (n = 149) and TST was carried out in: 129, 156, 147, 148 and 121 subjects respectively. In each group the agreement and kappa coefficient between QFT-GIT and TST at 5, 10, 15 mm of TST diameter was analyzed.

Results: We observed high prevalence of LTBI in relevant studied groups: 37% (n = 58,7% (0,26); 60,7% (0,34); 75,4% (0,45); 2: 55,8% (0,20); 60,9% (0,24); 70,0% (0,23). Agreement and kappa at 5, 10, 15 mm of TST cut-off in each group were: in group 1: 58,7% (0,26); 60,7% (0,34); 75,4% (0,45); 2: 55,8% (0,20); 60,9% (0,24); 70,0% (0,23).

Conclusions: TST was characterized by lower diagnostic value in Polish population vaccinated and revaccinated with BCG but TST cut-off 15 mm and more should be considered for diagnosis of LTBI because of highest agreement with QFT-GIT.

P304
Indeterminate IGRA results in routine practice
Peter Kewin1, Teresa Inkster2, Brian Choo-Kang3.

Introduction: Interferon-γ release assays (IGRAs) are used in the diagnosis of latent TB, but up to 6.1% yield an indeterminate test result (ITR; Diel Chest 2009). IGRA's are not currently used for diagnosis of active TB (Sester ERJ 2011). We determined the indications for T-Spot.TB and frequency of ITRs in our routine practice.

Methods: Patient records were reviewed for all T-Spot.TB tests performed in Glasgow (May 07 - June 08). Data was collected on patient demographics, clinical assessment, reasons for request and final diagnosis.

Results: T-Spot.TB was performed on 303 patients (see table 1). The rate of ITRs on first testing was 55/303 (18.2%). Almost half were performed for active TB (45%), and symptoms suggestive of active TB increased the positivity of ITRs. Frequency of ITRs varied between hospital (2.34%) and specialty (0.40%) (data not shown). Female sex, Asian race, ex or non-smoking status, excess alcohol and age >75 favoured an ITR. Immunosuppressive drugs had no effect, although patients with ITR had a slightly lower lymphocyte count. Of the 26 tests repeated, 14 were negative, 6 positive and 4 ITR. Overall 35/103 (11.5%) of patients had an ITR. On follow up 31/35 had no TB, and 4/35 latent, presumed clinical or confirmed TB.

Conclusions: ITRs were more common than in other studies, and may be influenced by patient factors and system failures. Inappropriate testing was common and may be minimised by further educating staff requesting and performing tests.

P305
Detection of IFN-γ responses for diagnosis of tuberculosis infection in chronic inflammatory disease patients
Irene Latorre1,2, Sonia Minguez3,6, Irene Latorre1,5,6, Sonia Minguez2, Marta Vilavella3, Jessica Diez1, Jose Manuel Carraconsa1,2, Cristina Pratt1,5, Lourdes Mateos2, Eugeni Domench6, Vicente Ausina1,5,6, Carlos Ferrandiz5,5, Jose Dominguez1,5,6, Servei Microbiologia, Hospital Universitari Germans Trias i Pujol, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 2Servei Reumatologia, Hospital Universitari Germans Trias i Pujol, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 3Servei Reumatologia, Hospital Universitari Germans Trias i Pujol, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 4Servei Digestiu, Hospital Universitari Germans Trias i Pujol, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 5Servei Dermatologia, Hospital Universitari Germans Trias i Pujol, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 6Servei Digestiu, Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain; 7CIBER Enfermedades Respiratorias, Instituto de Salud Carlos III, Badalona, Barcelona, Spain; 8CIBER Enfermedades Hepáticas y Digestivas, Instituto de Salud Carlos III, Badalona, Barcelona, Spain

Objective: Determine IFN-γ responses for latent tuberculosis infection (LTBI) diagnosis in chronic inflammatory disease patients.

Material and methods: 89 chronic inflammatory disease patients were classified in 3 groups. Group 1: 53 patients with rheumatic diseases scheduled for anti-TNF-α treatment. Group 2: 53 postnosis patients, 39.1% were receiving biologic treatments, and 43.5% classic systemic treatments. Group 3: 13 patients with Crohn disease, treated with immunosuppressors. TST was done in all cases. We determined IFN-γ production with QuantiFERON-TB Gold In Tube (QFN) and T-SPOT.TB (TS.TB).

Results: Group 1: TS.TB, QFN and TST were positive in 20.8%, 17% and 13.2% respectively. We obtained 4 QFN indeterminate results (7.5%) and 2 for TS.TB, QFN were positive in 5.6% and TST negative in all cases. Concordance between both IFN-γ assays and TST performed simultaneously, TS.TB and QFN were positive in 17.14% of the cases. In contrast, TST was positive in 21.74%. Five patients were documented with a previous positive TST. Therefore, when we analyzed patients with IFN-γ assays and TST performed simultaneously, TS.TB and QFN were positive in 5.6% and TST negative in all cases. Concordance between TS.TB and QFN was 100% Group 3: The three assays were negative in all cases. We observed one TS.TB indeterminate result (7.7%) and 2 for QFN (15.4%), corresponding with patients receiving azathioprine.

Conclusions: Concordance between both IFN-γ assays was good. Indeterminate results were higher in those patients with Crohn disease. IFN-γ assays, in combination with TST, are useful for the diagnosis of LTBI in patients with inflammatory diseases.

P306
Screening of HIV positive TB contacts with an interferon-gamma release assay in a congestate setting in Singapore
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We used the T-SPOT.TB assay in screening HIV positive contacts of infectious TB cases in the prison setting. The test is believed, on presumptive evidence, to be more sensitive than the tuberculin skin test and QuantiFERON-TB Gold In Tube assay in detecting latent TB infection. We report the screening of 47 HIV positive contacts around 3 infectious TB cases in the prison from 2008 to 2010. Exposure of the contacts occurred during the 1-hour daily activities. Identified contacts were screened for symptoms and examined for signs of active disease. Sputum tests for AFB smears and cultures, chest x-ray and
T-SPOT.TB assay were done. Diagnosis of latent TB infection was based on the T-SPOT.TB assay, after excluding active disease. Window peak typhli (18% of the cases were positive) was offered if the test was negative and stopped if the repeat test was positive. Test results done after 8-10 weeks of treatment was negative. The median CD 4 count was 343 c/e1 and 44.4% of them were on anti-retroviral therapy. 8 contacts had positive T-SPOT.TB assay result, 2 of whom had active TB (yield of 4.3%). The indeterminate rate was 2.1%. 3 contacts completed preventive treatment while 14 contacts had window peak typhli. During the mean follow up of 19 months (median of 21.5 months, range 0 to 25 months), one of the T-SPOT.TB assay negative contacts, whose CD4 count was 4 c/e1, developed active TB 11 months after completing screening.

Except in cases with extremely low CD count, the T-SPOT assay appears to have a good negative predictive value for progression to active disease in HIV positive TB contacts in Singapore.

P307 The role of interferon-γ release assay (IGRA) testing in a UK teaching hospital
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Background: IGRA's including T-SPOT (T-SPOT.TB)® have recently been adopted for the diagnosis of latent (LTBI) infection with Mycobacterium tuberculosis (MTB). They may also have a role in ruling out active tuberculosis; however a recent meta-analysis has suggested that its specificity may not be high enough to exclude active disease [1].

Aims and objectives: The aim of this study was to retrospectively evaluate the use of the T-SPOT assay at a UK University Teaching Hospital to determine i) the indications for which it is being utilised and ii) whether its use led to any change in management.

Methods: Patients having T-SPOT performed between 09/2008 and 02/2010 were retrospectively identified from our TB database. Information regarding test indication, patient demographics and imaging results was collected from case notes and picture archiving and communications system (PACS). Change in patient management as a result of the T-SPOT was noted (as judged by two clinicians).

Results:

<table>
<thead>
<tr>
<th>Indication for T-SPOT</th>
<th>Total number of patients</th>
<th>Positive</th>
<th>Negative</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immigrant screening</td>
<td>30</td>
<td>16</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Contact tracing</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Healthcare worker screening</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Exclusion of active disease</td>
<td>53</td>
<td>19</td>
<td>25</td>
<td>9</td>
</tr>
</tbody>
</table>

Forty-three (45%) of T-SPOT tests were performed to exclude LTBI and 53 (55%) to exclude active disease. The T-SPOT result led to a change in management in 42 (44%) of cases. To the best of our knowledge no patients with a negative T-SPOT result were subsequently diagnosed with active MTB infection.

Conclusion: In addition to excluding LTBI, T-SPOT can be a useful investigative tool in helping clarify the clinical picture in cases of suspected active TB.


P308 Quantiferon testing in British army recruits
Rachel Mackley, David Spence.

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Our hospital has links with an Army base and investigates recruits for Tuberculosis (TB). Many come from high prevalence areas. Recruits are screened with a Mantoux test. Those with a Mantoux reaction ≥15mm and no previous BCG vaccination are referred for Quantiferon Gold testing. If positive they are treated for latent TB. We reviewed referrals over a 2 year period (April 2008 - April 2010) to assess compliance with Army policy and investigate whether referral based on Mantoux reaction alone is warranted.

Demographic data were gathered from Army records. The relationship between Quantiferon and Mantoux results by Nationality

<table>
<thead>
<tr>
<th>Nationality</th>
<th>Quantiferon results</th>
<th>Mantoux reaction (mm range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepali</td>
<td>44</td>
<td>32 (73) 12 (27) 11 (6-21)</td>
</tr>
<tr>
<td>African</td>
<td>65</td>
<td>47 (72) 18 (28) 12 (6-22)</td>
</tr>
<tr>
<td>British</td>
<td>10</td>
<td>6 (60) 4 (40) 10.5 (6-15)</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>4 (66) 2 (33) 10.5 (6-15)</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>89 (71) 36 (29)</td>
</tr>
</tbody>
</table>

A positive Quantiferon test and a Mantoux reaction of ≥15mm was assessed using a Chi-squared test.

153 cases were identified, 28 were excluded due to insufficient data, leaving a sample of 125. All cases were male. Median age was 21.5 years (range 17-53). For analysis, recruits were divided into 4 areas (see table 1).

99 recruits (79%) had a positive Quantiferon test. There was no significant relationship between Quantiferon positivity and Mantoux size ≥15mm (p=0.093). Large numbers of recruits are referred based on their Mantoux results, including many with reactions of 6-14 mm. As there was no significant relationship between the rate of Quantiferon positivity and Mantoux reaction size ≥15mm, referral decisions should not be made on this basis alone.

Further research is warranted to assess the current referral guidelines.

P309 Evaluating the use of the interferon-γ response to mycobacterium tuberculosis (MTB) specific antigens to diagnose latent tuberculosis infection in patients with chronic inflammatory joint and skin diseases
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Introduction: The treatment of chronic inflammatory diseases has been transformed with targeted biologic therapies. Patients receiving this treatment are at increased risk of reactivating latent tuberculosis infection (LTBI). Tuberculin skin test (TST) has been the gold standard for detecting latent LTBI, but may be difficult to interpret in patients receiving immunosuppressive therapies. In vitro interferon-gamma-release assays (IGRA) are an alternative.

Methods: A prospective cross-sectional study was conducted at an inner London tertiary referral centre. Patients were screened for LTBI and a TST was performed. Venous blood samples were obtained for QFR and TSTB.

Results: 102 patients were included, aged between 18 and 83 years. A total of 2% of patients were receiving at least one immunosuppressive therapy. A TST result was available in 84 patients. The overall agreement between the QFR vs TSTB excluding the indeterminate results was 69 out 78 (k=0.572), between QFR vs TST was 62 out of 79 (k=0.241) and between TSTB vs TST was 58 out of 72 (k=0.304). 13 patients received chemoprophylaxis for presumptive LTBI.

Conclusion: Our study showed variation in results obtained from TST and IGRA's when used in our population, some of whom were immune compromised. For patients where interpretation of the results may prove challenging, LTBI screening tests may be best used in combination.
some nationalities and in pts with TST>15 mm, partly decreasing the economic advantage of its use to reduce PTs. Better information on QFT role could be obtained extending this program to H5 with TST <5 mm or age ≥36 yrs but QFT technicalities and heath-care budget cuts do not allow this wider on-field application.

P311
Practical use of quantiferon test in Norway's largest TB-clinic
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Introduction: Since November 2008, Norway's largest TB-clinic (Diagnosesasjön, Oslo University Hospital, Ullevål) has implemented Quantiferon-TB GOLD In-Tube test (QFT) as a supplement to tuberculin skin test (TST).

Aims & objectives: The aim of our study was to evaluate clinical use and consequences of QFT results for the patient.

Methods & design: Patients with conclusive QFT result between November 2008 and December 2009, were included in this retrospective cross-sectional study.

Results: 415 patients were included and categorized by reason for referral: Immigrants (31.1%), School children (49.6%), Immunomodulation (7.5%), TB-Contacts (10.6%), Other (1.2%). Only 14 (3.4%) patients had negative TST (Mantoux<5mm). 124 (29.9%) patients had positive Quantiferon test. While 70 (56.9%) Immigrants had positive QFT, 33 (16%) of the School Children had positive QFT result. A multivariate analysis showed that the independent risk factors of a positive QFT test were higher age, reported TB-exposure, high-incidence TB region of birth and immigrants. QFT positivity was associated with age group >35 (OR 3.5) compared to age group <14, reported TB-exposure (OR 4.5), and high-incidence TB region of birth (OR 3.84). QFT result was the single most important decisionmaking. Though QFT has reduced numbers of patients given treatment in-Tube test (QFT) as a supplement to tuberculin skin test (TST).

Conclusions: QFT result was the single most influencing factor on the clinicians decisionmaking. Though QFT has reduced numbers of patients given treatment and follow-up, it is important to keep in mind the limited sensitivity of QFT in certain patient groups when interpreting the QFT results.

54. Genetic and environmental risk factors for respiratory diseases

P312
Late-breaking abstract: The forgotten majority: A decrease in persistent but not in intermittent asthma in a large cohort study
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Aim: To evaluate asthma prevalence and severity in Israeli teenage boys over the last decade.

Methods: A representative sample of three hundred thousand medical records of 17-year-old boys, who underwent a comprehensive medical evaluation for eligibility for national service between 1999 and 2008, were reviewed regarding asthma diagnosis and severity. Also monitored in this period were asthma hospitalization rate, corticosteroids inhalers (CSI) sales rates and air pollution in central cities.

Results: Lifetime asthma prevalence decreased from 9.66% to 8.12%. Mild persistent asthma prevalence decreased from 3.4% to 2.4% and moderate to severe asthma from 0.9% to 0.4%. Intermittent (3.5%) and inactive asthma (2%) remained stable.

Asthma hospitalization rate in 15-24 year-old males decreased from 5.2 to 3.2 per 10,000 hospitalizations. A significant increase in annual CSI sales rates and a decrease in NO2 and SO2 air concentrations were noted.

Conclusions: Prevalence of persistent asthma in Israeli 17-year-old boys decreased significantly over the last decade. Some of this decrease may be attributed to an increase use of CSI and a decrease in air pollution.

P313
Rare alpha-1 antitrypsin mutations in the Irish population
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AAT deficiency (AATD) results from mutations in the SERPINA1 gene, classically presenting with early-onset emphysema and liver disease. The most common mutation causing AATD is the Z mutation, with the S mutation weakly associated with liver disease. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ATS/ERS guidelines advocate screening all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as first degree relatives of known AATD patients. 5,000 individuals were screened following ATS/ERS guidelines as part of the Irish national targeted detection programme. AAT levels were determined by nephelometry. AAT phenotyping was performed by isoelectric focussing. Patient DNA isolated from DBS samples was genotyped by PCR (Roche LightCycler). Rare and novel mutations were identified by DNA sequencing of the SERPINA1 gene. A number of rare SERPINA1 mutations including I, V, F, X, Chotranch, Zonis, and Mmalton were identified. The I mutation (Arg9Cys) was present at a relatively high frequency (0.0038) in a targeted population, with over 40 cases identified. In addition, a new SERPINA1 mutation was identified.

Current testing of suspected AATD cases is often limited and can miss rare and novel clinically significant SERPINA1 mutations. The rare mutations described in this study were not detected by a commonly used genotyping assay, however, the low AAT levels prompted their correct identification using more detailed genetic analysis. Our findings underline the need for a comprehensive diagnostic workup of all patients with low AAT levels including phenotyping, genotyping and if necessary, DNA sequencing of the SERPINA1 gene.

P314
Hedgehog-interacting protein (HHIP) polymorphisms and chronic obstructive pulmonary disease (COPD)
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1Epidemiology, University Medical Center Groningen, Groningen, Netherlands; 2Pulmonology, University Medical Center Groningen, Groningen, Netherlands; 3Pulmonology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands; 4Pathology, University Medical Center Groningen, Groningen, Netherlands; 5Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands

Genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in the region of Hedgehog interacting protein (HHIP) to be associated with COPD, level of lung function and height in the general population. We aim to investigate the association of rs1032295 and rs13147758 with lung function level and decline in subjects from the general population, as well as the association with lung function level and decline and small airways function in subjects with established COPD.

Two SNPs rs1032295 and rs13147758 in the HHIP region were genotyped in 1,152 subjects from the general population (Doetinchem) and 110 COPD patients (GLUCOLD). Associations of the SNPs with lung function level and small airways function (FEV1 and FEF25-75%) at baseline were analyzed using linear regression.
Low-fat yoghurt intake was directly related to increased risk of both heritable and non-heritable factors in the population but not with lung function decline. Moreover, SNPs in the HHIP region associated significantly with lung function decline in individuals with established COPD patients, suggesting a possible protective effect of the gene in COPD patients.

Background: Dairy products are important sources of micronutrients, fatty acids, and probiotics that could modify the risk of child asthma and allergy development.

Objective: To examine associations of dairy intake during pregnancy with child asthma and atopic dermatitis (AR) at 7 years in the Danish National Birth Cohort.

Methods: Data on milk and yoghurt consumption was collected in mid-pregnancy using a validated FFQ (N=61,912). We assessed asthma and AR through questionnaires and registry linkages. Current asthma was defined as self-reported asthma diagnosis and use of asthma medication in the past 12 months. We conducted multiple logistic regression and report here odds ratios with 95% CI.

Results: At 7 years 5.9% (N=2,316/39,059) of children had registered lifetime asthma diagnosis and 4.2% (N=1,574/37,347) reported current asthma. Life-time AR diagnosis was 0.5% (N=191/39,059) using the registry and 4.9% (N=1,887/38,763) by self-report. Total milk intake was inversely related to current asthma risk (<100ml/day vs. ≥1l/day) = OR 1.12, 95% CI 1.04, 1.20). For yoghurt intake, children of women who ate low-fat yoghurt (with fruit) had a 22% lower risk of asthma (vs. no yoghurt) = OR 0.78, 95% CI 0.65, 0.94). For yoghurt intake, children of women who ate low-fat yoghurt (with fruit) had a 22% lower risk of asthma (vs. no yoghurt) = OR 0.78, 95% CI 0.65, 0.94). For yoghurt intake, children of women who ate low-fat yoghurt (with fruit) had a 22% lower risk of asthma (vs. no yoghurt) = OR 0.78, 95% CI 0.65, 0.94).

Conclusion: Low-fat yoghurt intake was directly related to increased risk of both child asthma and AR, while total milk intake appeared to be protective. Non-fat related nutrient components in yoghurt may be mediating this increase in risk.

PH16
Heritability of atopic dermatitis: Population study and systematic review
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Aims: To investigate heritability and dependence of asthma from the Danish Twin Registry. We performed a systematic review of the literature to obtain thorough estimates of the heritability of the disease.

Methods: In a population-based questionnaire study of 19,748 child and adolescent twins from the Danish Twin Registry, we calculated concordance rates and heritability of atopic dermatitis. We performed a systematic review of the literature to obtain thorough estimates of the heritability of the disease.

Results: The overall prevalence of atopic dermatitis in the population was 17.8% among girls and 14.7% among boys, p<0.001. The concordance rate for atopic dermatitis was significantly higher in monozygotic than in dizygotic twins; 0.80 vs. 0.41 among girls and 0.74 vs. 0.37 among boys. The overall heritability of atopic dermatitis was the same in boys and girls; 93% (90-94%) with the remainder of the phenotypic variance ascribable to non-shared environmental factors.

Conclusions: Atopic dermatitis is a highly heritable disorder. Compared with estimates from systematically identified studies the heritability of atopic dermatitis in the Danish population is substantial.

PH17
Remission of childhood asthma in adolescence – A longitudinal study
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Background: Few population-based studies have prospectively evaluated remission of childhood asthma and factors related to remission.

Aims: To investigate remission and determinants of asthma remission from the age of 7-8 years to 19 years.

Methods: In 1990, a questionnaire about asthma and related conditions was distributed to all children 7-8 years old in three municipalities in Northern Sweden, and 3,430 (97%) participated. After a validation study, 2,48 (7.2%) of the children were defined as having current asthma. The 248 children were reassessed by annual questionnaires until the age of 19 years where 205 (83%) participated. During the follow-up period spirometry, bronchial challenge testing and skin prick tests were performed.

Results: At the age of 19 years, 76 out of the 205 participants (37%) were in remission defined as no wheeze and no use of asthma medication during the last 12 months. A negative skin prick test at age 7-8 years and male sex were significant predictors for remission. OR: 2.1 (CI 95% 1.1-4.2) and 2.3 (CI 95% 1.2-4.1), respectively. Having rhinitis or eczema at age 7-8 years was negatively associated with remission. Neither heredity for asthma nor parental smoking or rural living was associated with remission.

Conclusion: Remission of childhood asthma in late teenage years was common and related to absence of allergic sensitization and other allergic diseases. The higher rate of remission among boys contribute to the switch in boy-to-girl prevalence ratio from asthma being more common among boys in childhood to being more common among girls/women later in life.
of asthma was observed in rare/never drinkers, OR=1.45 (1.17-1.82), p<0.001, whereas the risk of asthma in heavy daily drinkers was also increased, however not statistically significant, OR=1.26 (0.63-2.50), p=0.514. After adjustment for overall intake of alcohol, preference for beer drinking was associated with an increased risk of asthma compared with no preference, OR=1.29 (1.03-1.61), p=0.01.

**Conclusions:** Alcohol intake appears to increase the risk of new-onset asthma in adults with a U-shaped association between amount of alcohol intake and the risk of asthma.

**P320**

Aspirin-induced asthma is strongly associated with obesity: Large population study on prevalence and risk factors

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**Background:** Population-based studies on aspirin-induced asthma are few and no comprehensive risk factor analysis for the condition has been published. We sought to investigate the prevalence and risk factors of aspirin-induced asthma in the general population.

**Methods:** A questionnaire on respiratory health was mailed to 30 000 randomly selected subjects aged 16-75 years in West Sweden, 29 218 could be traced and 18 087 (62%) responded. The questionnaire included questions on aspirin-induced dyspepsia, asthma, respiratory symptoms and possible determinants.

**Results:** The prevalence of aspirin-induced asthma was 0.5%, 0.3% in men and 0.6% in women (p=0.014). The prevalence increased with increasing body mass index (BMI<20: 0.3% vs. BMI>35: 2.2%, p<0.001).

**Conclusions:** Aspirin-induced asthma was common in the population. Increasing body mass index increased the risk of aspirin-induced asthma in a dose-response manner. A number of risk factors including obesity were considerably stronger for aspirin-induced asthma than for aspirin-tolerant asthma.

**Figure 1. Prevalence of aspirin-induced asthma by body mass index.**

![Figure 1](https://example.com/figure1.png)

Obesity was a strong risk factor for aspirin-induced asthma (BMI<35: OR 8.15; 95% CI 1.67-5.76). Obesity, occupational exposure to dust gases or fumes and visible mold at home were stronger risk factors for aspirin-induced asthma than for aspirin-tolerant asthma. Current smoking was a risk factor unique for aspirin-induced asthma (OR 2.70; 95% CI 1.52-4.81).

**Conclusion:** Aspirin-induced asthma was common in the population. Increasing body mass index increased the risk of aspirin-induced asthma in a dose-response manner. A number of risk factors including obesity were considerably stronger for aspirin-induced asthma than for aspirin-tolerant asthma.

**P321**

Physical fitness and asthma development in a random population during three decades. The Odense schoolchild study

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**Aim:** To investigate the longitudinal association between physical fitness and the development of asthma and asthma-like symptoms in a general population sample. 1609 children from the Odense schoolchild study were assessed from 1985 to 2007 at age 9, 15, 20 and 29 years. The same physical fitness test was applied at all occasions and fitness was stratified into quintiles for each sex.

**Results:** The following analysis is based all subjects who performed a satisfactory fitness test: 1369 children at age 9 (mean 9.7), 1072 (78%) at age 15 (mean 15.6), 881 (64%) at age 20 (mean 20.3) and 814 (60%) at age 29 (mean 29.3) performed a satisfactory fitness test respectively. The results showed that fitness levels at each age was associated with lower lung function at same age (p<0.001). The was no significant difference in the occurrence of asthma-like symptoms in the sex specific fitness quintiles at age 9 years. Higher fitness at age 9 was associated with a lower occurrence of asthma at age 20 (p=0.001) and 29 years (p=0.04) as well as significant at age 15 years. On the other hand, at age 15 there was a significant trend of higher occurrence of asthma-like symptoms the lower the fitness quintile at age 9 years (p<0.05). In the sex specific analyses the association between physical fitness at age 9 years and asthma at age 20 and 29 years was only significant in women (age 20; p=0.01); (age 29; p=0.04) and men (age 20; p=0.07); (age 29; p=0.7) respectively.

**Conclusion:** In conclusion, our results point toward the importance of a moderate-high fitness level before puberty to reduce the risk of asthma development in adulthood but this effects seems mainly present in women.

**P322**

Impact of physical inactivity on cognitive function in adults with obstructive lung disease (OLD)

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**Background:** OLD may increase risk of cognitive deficits.

**Objective:** Examine the role of physical inactivity in cognitive impairment (CI).

**Methods:** Members of a population-based cohort with self-reported physician-diagnosed COPD, emphysema, or chronic bronchitis (n=140; 63% female, mean age 67 yrs, 19% current smokers) completed baseline (T1) and 2-year follow-up (T2) in-person assessments that included spirometry; completion of the CHAMPS Questionnaire to estimate energy expenditure in vigorous/moderate intensity activities (M/V) and overall; and a 10-test cognitive battery. We defined physical inactivity as no expenditure in M/V activities. We transformed cognitive test scores to age-adjusted z-scores and defined CI as z-scores ≤ −1.5 or ≥ +3.3 of cognitive tests. Logistic regression tested relationships between physical inactivity and CI at both T1 and T2, controlling for sex, education, smoking, comorbid conditions, low O2 saturation, depression and lung function.

**Results:** At T1, 31% were physically inactive. CI was more frequent among inactive subjects (27% vs. 12%; adjusting for covariates: OR=9.8 [95% CI 1.8, 53.1]). Adjusting for covariates plus T1 CI, inactive subjects were more likely to be cognitively impaired at T2 (OR=4.4 [1.2, 15.8]). Among 120 subjects not impaired at T1, inactive subjects were more likely to develop CI at T2 (26% vs. 15%; OR=6.0 [1.5, 24.1]).

**Conclusion:** Physical inactivity is a significant risk factor for presence and incidence of cognitive impairment among adults with OLD. Clinical relevance: In OLD, participation in a even moderate physical activity may offer protection from cognitive impairment.

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**P323**

Decrease in smoking is related to a decrease in respiratory symptoms but not asthma

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**Background:** In 2005, smoking was banned in public places in Sweden.

**Aim:** To compare the prevalence of respiratory symptoms and asthma among adults in 1996 and 2006 by smoking habits.

**Methods:** In 1996, 7104 randomly selected subjects (response rate 85%) in North Sweden aged 20-69 answered a postal questionnaire including questions about respiratory symptoms, and smoking habits. Correspondingly, in 2006 a new sample of 6165 subjects (77% responded) of same age answered the same questionnaire.

**Results:** All respiratory symptoms were strongly related to smoking. The prevalence of most respiratory symptoms decreased significantly from 1996 to 2006 parallel to a decrease in smoking, which decreased from 27 to 19%. The prevalence of spumon production decreased from 19.1 to 15.0%; longihooding cough 12.4-10.8%; chronic bronchitis 7.4-6.3% and recurrent wheeze 13.4-12.1%. The prevalence of these symptoms was similar among smokers, and decreased among non-smokers. Physician-diagnosed asthma increased among both smokers and non-smokers, totally from 9.3 to 11.5%. However, the proportion of medicine users and symptomatics among the asthmatics were lower in 2006. In multivariate analysis adjusted for confounders, a significant increase of asthma by study year was found (OR 1.4). Corresponding analysis for chronic bronchitis yielded a significant decreesenct effect by study year (OR 0.8).

**Conclusions:** The decreased prevalence of respiratory symptoms was parallel to a decrease in smoking. The decrease in bronchitis symptoms among non-smokers may be related to a reduction of environmental tobacco smoke and occupational airborne exposures. Increased diagnostic activity can explain the increase in asthma.

**P324**

Recent trends in COPD prevalence in Italy

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**Aim:** To compare prevalence rates and risk factors associated with COPD in an Italian population sample surveyed 20 years apart.

**Methods:** The family cluster random sample living in Central Italy (Pisa) was enrolled in 1991-93 (n=2529, age range 20-97 yrs, males 44.4%); the survivors, with the inclusion of new family members, were studied again in 2009-10, within the framework of the European Union funded project IMCA2 (Indicators for Mon-
by questionnaire. Spirometry was also used. A Logistic Regression analysis was ran to assess the association between COPD diagnosis and risk factors. 

**Results:** COPD diagnosis prevalence had increased from 8.2% to 11.1% over the 20 years. In both studies, COPD diagnosis is significantly associated with 64+ yrs (IS: OR 15.8, CI 95% 7.7-32.5; ISS: OR 6.1, CI 95% 3.1-11.9) and 45-64 yrs age range (IS: OR 8.6, CI 95% 4.2-17.4; ISS: OR 2.3, CI 95% 1.4-8.4), male gender (IS: OR 19.5, CI 95% 1.4-5.2; ISS: OR 1.5, CI 95% 1.0-2.4), actual or past smoking habits (IS: OR 2.6, CI 95% 1.7-4.1; ISS: OR 1.9, CI 95% 1.2-3.0), work exposure to dust, gas or chemicals (IS: OR 3.1, CI 95% 1.4-6.9; ISS: OR 1.8, CI 95% 1.2-2.7), co-presence of asthma diagnosis (IS: OR 5.9, CI 95% 3.8-9.3; ISS: OR 4.5, CI 95% 3.0-6.6) and cardiovascular illness (IS: OR 2.3, CI 95% 1.6-3.2; ISS: OR 2.5, CI 95% 1.5-4.0).

**Conclusions:** COPD is still increasing in Italy. While the association with the risk factors is confirmed, there is a general decrease of the OR values over the 20 years. The OR decline for male gender is in line with the recent raise of COPD prevalence in females.

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**P325**

COPD among never-smokers

Stig Hagstål1, Linda Ekerlung1, Anne Lindberg1, Eva Ronnmark1

**Aim:** To study the prevalence and risk factors of COPD among never smokers and to determine the proportion of never smokers among subjects with COPD.

**Methods:** Of 5189 postal questionnaire respondents (response rate 88%) aged 46-77 years, a stratified sample of the general population of Norrbotten, Sweden, a random sample of 1500 subjects were invited to structured interviews and lung function tests, and 1237 completed a lung function test with acceptable quality. Never smokers were defined as those who had smoked <1 cigarette/day for <5 years. COPD was defined as GOLD stage ≥II, as several medical conditions are associated with a FEV1/FVC <0.7.

**Results:** The prevalence of COPD among non-smokers was 3.4% and tended to be more common among women than men (4% vs 2.3%; NS) and was strongly age related particularly among men. For comparison the overall prevalence in ages ≥45 y COPD was 8.1% (similar in men and women). Among never smokers the prevalence of severe COPD (FEV1<50% of predicted) was 0.8 (women 0.9%; men 0.6%; NS). In contrast to men, severe cases of COPD were found among women aged >65 years. Of all men with COPD, 15% were never smokers versus twice that much among women. Increasing age was a significant risk factor, while passive smoking, manual work in industry and female sex tended to be associated with COPD among never smokers.

**Conclusion:** The prevalence of clinically relevant COPD among never smokers aged >45 y was 3.4% and was associated with increasing age. One out of seven men with COPD versus one out of three women had never been smokers.

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**P326**

BMI and risk for death in COPD

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**Aim:** To study the long-term outcome of BMI-levels in a cohort of COPD subjects derived from a study of the general population.

**Methods:** A stratified sample of subjects from a population survey was invited to clinical examinations including lung function tests in 1986. Out of 1506 (91% of the invited) we identified 266 subjects, 64% men, fulfilling the spirometric GOLD criteria of COPD. The subjects with COPD reflected well COPD in the general population of a stratified sample of the general population of Norrbotten, Sweden, a random sample of 1500 subjects were invited to structured interviews and lung function tests, and 1237 completed a lung function test with acceptable quality. Never smokers were defined as those who had smoked <1 cigarette/day for <5 years. COPD was defined as GOLD stage ≥II, as several medical conditions are associated with a FEV1/FVC <0.7.

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**Conclusion:** The prevalence of clinically relevant COPD among never smokers aged >45 y was 3.4% and was associated with increasing age. One out of seven men with COPD versus one out of three women had never been smokers.

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**P327**

Cured meats consumption increases risk of readmission in COPD patients

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**Aim:** To study the prevalence and risk factors of COPD among never smokers and to determine the proportion of never smokers among subjects with COPD.

**Methods:** Of 5189 postal questionnaire respondents (response rate 88%) aged 46-77 years, a stratified sample of the general population of Norrbotten, Sweden, a random sample of 1500 subjects were invited to structured interviews and lung function tests, and 1237 completed a lung function test with acceptable quality. Never smokers were defined as those who had smoked <1 cigarette/day for <5 years. COPD was defined as GOLD stage ≥II, as several medical conditions are associated with a FEV1/FVC <0.7.

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**Conclusion:** The prevalence of clinically relevant COPD among never smokers aged >45 y was 3.4% and was associated with increasing age. One out of seven men with COPD versus one out of three women had never been smokers.

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**P328**

Professional exposure to goats increases the risk of pneumonic-type lung adenocarcinoma. Results of the IFCT-0504-epidemio study

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**Aim:** To study the prevalence and risk factors of COPD among never smokers and to determine the proportion of never smokers among subjects with COPD.

**Methods:** A stratified sample of subjects from a population survey was invited to clinical examinations including lung function tests in 1986. Out of 1506 (91% of the invited) we identified 266 subjects, 64% men, fulfilling the spirometric GOLD criteria of COPD. The subjects with COPD reflected well COPD in the general population of a stratified sample of the general population of Norrbotten, Sweden, a random sample of 1500 subjects were invited to structured interviews and lung function tests, and 1237 completed a lung function test with acceptable quality. Never smokers were defined as those who had smoked <1 cigarette/day for <5 years. COPD was defined as GOLD stage ≥II, as several medical conditions are associated with a FEV1/FVC <0.7.

**Results:** The prevalence of COPD among non-smokers was 3.4% and tended to be more common among women than men (4% vs 2.3%; NS) and was strongly age related particularly among men. For comparison the overall prevalence in ages ≥45 y COPD was 8.1% (similar in men and women). Among never smokers the prevalence of severe COPD (FEV1<50% of predicted) was 0.8 (women 0.9%; men 0.6%; NS). In contrast to men, severe cases of COPD were found among women aged >65 years. Of all men with COPD, 15% were never smokers versus twice that much among women. Increasing age was a significant risk factor, while passive smoking, manual work in industry and female sex tended to be associated with COPD among never smokers.

**Conclusion:** The prevalence of clinically relevant COPD among never smokers aged >45 y was 3.4% and was associated with increasing age. One out of seven men with COPD versus one out of three women had never been smokers.
any cancer (OR=3.43, 95% CI: 1.10-10.72, p = 0.034), and professional exposure to goats (OR=5.09, 95% CI: 1.05-24.69, p = 0.043).

Conclusions: This exploratory case-control suggests a link between professional exposure to goats and P-ADC, and prompts for further epidemiological evaluation of potential environmental risk factors for P-ADC.

63. Mechanism and monitoring of airway diseases

353 Longitudinal analysis of lung function decline with eosinophilic clustering in severe asthma
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Background: Lung function decline over time is an important variable for patients with severe/ﬁced asthma and it is unclear how granulocytic cell counts in sputum are associated with this variable as few longitudinal studies include both biomarkers.

Aims and objectives: To analyse lung decline, post bronchodilator FEV1 was recorded over time in order to determine the best ﬁtting mixed effect model to determine the role of granulocytes.

Methods: Data was collected from the Glenﬁeld Hospital Severe asthma clinic, the mean duration of follow up and number of visits was 6 years and 2.75 years. A mixed effect model was applied to the data. Using individual patient mean and standard deviation over time, a statistical mixture/cluster analysis was implemented.

Results: For the best ﬁtting mixed effects model FEV1 decline was -257mL/year (p=0.0001). The signiﬁcant independent ﬁxed effects included exacerbations, age of onset, log eosinophils (p<0.001). Three clusters were found in the log eosinophil cluster analysis. Cluster 1 described a low grade eosinophilic group. Cluster 2, a hyper eosinophilic group and cluster 3, a neutrophilic/non-eosinophilic group. The clusters differed in their frequency of exacerbation/decline.

Conclusions: Eosinophils were found to be a signiﬁcant predictor for FEV1 decline. Clustering eosinophil variables found that patients are either consistently eosinophilic over time or have a large amount of eosinophilic variation.

354 Sputum eosinophilia identiﬁes systemic corticosteroid responsiveness in acute exacerbations of COPD
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Introduction: Eosinophilic airway inﬂammation (EA, ≥3% sputum eosinophils) during stable chronic obstructive pulmonary disease is associated with corticosteroid responsiveness. Whether this is true during exacerbations remains unknown.

Methods: COPD patients were entered into a double blind prednisolone placebo controlled trial. Measurements of airway inﬂammation, lung function and health status using the chronic respiratory questionnaire (CRQ) and visual analogue scale (VAS) were assessed at baseline, exacerbation and 2 weeks after treatment.

Results: 166 exacerbations were captured from 109 patients (69 men, 40 women). All eosinophilic exacerbations (n=31) were treated with prednisolone. Non eosinophilic airway inﬂammation (NEA) occurred in 135 exacerbations, of which 70% (n=94) were treated with prednisolone and 30% (n=41) with placebo. Two weeks after prednisolone treated exacerbations, quality of life and lung function improved signiﬁcantly in those with EA compared to NEA (mean change, 95%CI in CRQ and FEV1, was 1.5 units (1.1 to 1.9) vs. 0.8 units (0.5 to 1.0) (p<0.001) and 335mL (219 to 451) vs. 102mL (52 to 152) (p<0.001) respectively. VAS returned to baseline earlier in EA exacerbations treated with prednisolone (p=0.016, see ﬁgure)

Conclusion: Corticosteroid responsiveness during exacerbations of COPD can be identiﬁed by a sputum eosinophilia.

355 Tapering oral corticosteroids in severe asthma is associated with a decrease in fractional exhaled nitric oxide
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Rationale: In a recent oral corticosteroid tapering study in patients with severe asthma (Hashimoto and Neijmu 2010), we observed high levels of exhaled nitric oxide (FENO) despite high doses of oral corticosteroids, and, unexpectedly (Smith NEJM 2005), only a minor role of FENO in adjusting the dose.

Hypothesis: Changes in FENO, values in patients with severe prednisone dependent asthmatics are not associated with changes in corticosteroid dose or clinical parameters.

Methods: 48 adult patients with severe, prednisone dependent asthma (mean SD age 49.4 (12.2) y; 18 male) were included in this 6 months follow-up study. Relationships between changes in daily FENO and oral corticosteroid dose, asthma control (ACQ), and FEV1 were assessed. Pearson correlation and regression analyses were used.

Results: Baseline median (range) FENO, and prednisone were 38 (2.5-3000) ppb and (0-60) mg/day. Daily changes in FENO from baseline were positively associ-ated with daily changes in prednisone dose (r=0.22, p=0.003) but not with FEV1 (r=0.02, p=0.77) or ACQ (r=0.03, p=0.65).

Conclusion: In contrast to patients with mild-moderate asthma, patients with severe, prednisone dependent asthma show a decrease in FENO levels when prednisone is tapered.

Implication: This suggests that oral corticosteroids may contribute to persistently high levels of FENO in severe asthma.

356 Sputum eosinophil levels in corticosteroid-treated asthmatic patients
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We have shown that asthmatic patients, despite being asymptomatic after 1-month treatment with inhaled corticosteroids (ICS), may have persistent sputum eosinophilia associated with higher degrees of bronchial hyperresponsiveness (Bacci et al., ATS meeting 2010). In order to test the effects of longer treatment periods, we treated 116 symptomatic, steroid-naive, mild-to-moderate asthmatic patients with different doses of ICS (50 to 500 mcg bid) for three to six months. Before and after treatment, all patients underwent spirometry, methacholine test, sputum analysis, and recorded symptom score (SS) and Peak Expiratory Flow (PEF) throughout the study period. Regardless of treatment dose and duration, some patients (n=56) still had high (≥2%) sputum eosinophils after ICS treatment; they were no different from patients with low sputum eosinophils as regards clinical and functional data after treatment, but had higher baseline SS (1.5 [0.1-3.6] vs 1.0 [0.1-3.1], p=0.04). After treatment, some patients still had high sputum eosinophils despite being totally controlled (SS=0); they were no different from totally controlled patients with low sputum eosinophils.

We conclude that, in patients with greater symptom levels before treatment, sputum eosinophilia may persist despite ICS treatment. Also, sputum eosinophilia may persist even in patients with totally controlled asthma, but after 6 months the...
**A double-blind randomised control trial of peripheral blood eosinophils to direct prednisolone use in COPD exacerbations**

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**Introduction:** COPD exacerbations and treatment responses are heterogeneous. Prednisolone therapy is associated with adverse events. Identifying steroid responsive subgroups may be beneficial.

**Aims:** To compare biomarker-directed prednisolone therapy to current standard treatment during COPD exacerbations.

**Methods:** Patients with COPD exacerbations were randomised to receive standard therapy (ST) or a biomarker-directed therapy (BT). ST patients were given prednisolone when the blood eosinophil count was ≥2% (biomarker positive) and placebo when ≤2% (biomarker negative) (see figure).

**Results:** From 109 patients; 86 exacerbations were treated in the BT group and 80 in the ST group. Prednisolone prescription was reduced by 49% (95% CI 38 to 59, p < 0.001) in the BT compared to ST group. There was no difference between groups in health status or FEV1 after 14 days treatment. Placebo administration did not result in excess treatment failure (hospitalisation or readmission) which occurred in 15% and 2% of biomarker negative patients in ST and BT groups (p = 0.04). Improvements in health status after 14 days were greater in placebo treated patients compared to those in the ST group who were biomarker negative (mean change 1.01 vs. 0.56; mean difference 0.45; 95% CI 0.01 to 0.90; p = 0.04).

**Conclusions:** A phenotype-specific biomarker approach can safely and effectively be applied to prednisolone therapy during exacerbations.

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**Disease expression in patients with primary ciliary dyskinesia (PCD), CF and pancreatic sufficiency (CF-PS) and insufficiency (CF-PI)**

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**Aim:** To correlate clinical status, microbiological, FEV1, and HRCT-Totol Brody Score (CT-TBS) between patients with CF-PI, CF-PS and PCD. Data on FEV1, HRCT, sputum cultures and BMI were collected as part of their routine assessment.

**Results:** Overall, 145 patients (79-CF-PI, 43-CF-PS, 23-PCD) participated in this study. The age of the CF-PS group was markedly higher compared to the other groups. BMI was notably lower in the PCD group compared to both CF groups. FEV1 had a strong negative correlation with age in the CF groups, not in the PCD groups. BMI was notably lower in the PCD group compared to both CF groups. FEV1 had a strong negative correlation with age in the CF groups, not in the PCD groups. BMI was notably lower in the PCD group compared to both CF groups.

**Conclusion:** In PCD, FEV1 does not correlate with age, BMI, rate of PA infection and CT-TBS. Therefore, opposed to CF, in PCD, FEV1 is not a reliable predictor of severity of lung disease. Further studies are needed to delineate the pathogenesis and progression of lung disease in PCD.
64 Cystic fibrosis: new insights of diagnosis, inflammation and detecting exacerbations

361 Intestinal current measurement (ICM) as a new diagnostic test for cystic fibrosis (CF)
Malena Cohen-Cymberknoh1,2, Yasmin Yaakob1,2, Eltaw Kerem1,2, David Shoeybl1,2, Joseph Rivlin1, Lea Bemm2, Elie Picard1,2, Micha Aviram1, Michael Wilschanski1,2,3 CP Center, Department of Pediatrics, Department of Pediatric Gastroenterology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; 2CF Center, Carmel Medical Center, Haifa, Israel; 3CF Center, Rambam Medical Center, Haifa, Israel; 4CF Center, Shaare Zedek Medical Center, Jerusalem, Israel; 5CF Center, Sonka Medical Center, Beer Sheva, Israel

Background: Like the nasal potential difference (NPD) test, ICM may be useful for the diagnosis of atypical CF. However, ICM is currently limited at all age stages.

Aim: To assess the diagnostic reliability of ICM in a large cohort of CF, healthy controls and patients with questionable CF.

Methods: Rectal biopsies were taken from 3 groups: known CF patients, healthy controls and patients with questionable CF. The last group had a variety of symptoms suggestive of CF: recurrent pneumonia, unexplained bronchiectasis, chronic diarrhoea and/or failure to thrive. ICMs were performed using standard protocols by mounting the rectal biopsy in an Ussing chamber and sequentially adding secretagogues while recording current changes.

Results: 100% of known CF patients and 11 patients had abnormal ICM results.

Conclusions: ICM tests may be useful in early diagnosis of CF when compared to the porous Blackburn test (p<0.001). ICM may also be useful to detect CF in patients with similar symptoms, but are not confirmed by other tests.

362 Regulation of ion transporters and airway surface dynamics by lipoxin in cystic fibrosis bronchial epithelium
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Aim: To study downstream effects of impaired IFN induction we investigated the expression of IFN-stimulated genes (ISGs) which are important for the production of antimicrobial proteins.

Methods: Epithelial CF and non-CF cell lines (UNCCF2T/UNCN2T, CFBE41o-/16HBE14o-) were cultured and infected with RV-16 and -1B at a MOI of 2. Gene expression of ISGs including MX1, NGAL, OAS and NOS2 was assessed by RT-PCR. Exogenous IFN-β and -α were added before and after infection.

Results: Expression of all ISGs was reduced in CF and control cells upon virus infection. CF cells expressed 100-1000 times less ISGs than control cells (all p<0.05). ISG expression and RV replication were inversely related (MXA: r=0.79, p=0.001). There was a positive correlation between ISG expression and IFN-β (r=0.5, p<0.004) and -α, a production (NOS2: r=0.65, p=0.01). Exogenous IFN increased expression of ISGs to the level of control cells, with a more pronounced effect of IFN-β.

Conclusions: ISG induction upon RV infection is deficient in CF indicating a profound impairment of the early innate antiviral response. Addition of exogenous IFN restores antiviral pathways in CF, suggesting a potential use of ISGs in the prevention or treatment of RV-induced CF exacerbations.

364 Association of FCN1 and FCN2 gene polymorphisms with earlier onset of chronic pseudomonas aeruginosa (Ps) colonisation in cystic fibrosis (CF) patients
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Background: CF is a multisystem disease with high degree of phenotypic variability especially in lung disease. Modifying genes of innate immunity may be involved in early onset of Ps colonisation.

Methods: 82 Single Nucleotide Polymorphisms (SNPs) in 22 genes contributing to the innate immunity (MBL2, MAS3 (MBL associated serine Protease) 1/2, FCN (Ficolin) 1/2, LBP (Lipopolysaccharide-binding Protein), CD14,TLR (Toll-like receptors 1-10) were genotyped in a cohort of 116 CF patients. (age 6-44 years)

Results: CF patients being heterozygous or homozygous for the mutant allele of both linked SNPs FCN1 (promoter) (A) and FCN2 (Q72Q) (exon 9) (G>A) are earlier colonised with Ps (p=0.01) and 2.7 fold increase in the risk of Ps colonisation is seen in CF patients homozygous for mutant allele of -64A>C polymorphism FCN2 (promoter) (p=0.033) and in patients having at least one mutant allele of the linked S258A (G>T) polymorphism FCN2 (p=0.057).

Conclusion: Mutant alleles of FCN1 (pro and Q272Q) and FCN2 (-64A>C and S258A) is significantly associated with earlier Ps colonisation. Mutant allele of polymorphism of TLR10 is associated with later onset of Ps colonisation.

365 The polyamine spermine is increased in cystic fibrosis airway secretions
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Rationale: Sputum arginase contributes to the nitric oxide (NO) deficiency in cystic fibrosis (CF) airways. Ornithine, the product of arginase activity, is the precursor of polyamines, which may play a role in the pulmonary response to injury and remodeling.

Objective: To measure concentrations of spermine in sputum of CF patients.

Methods: Using mass spectrometry, spermine was measured in sputum of clinically stable patients with CF (n=10), CF patients before and after antibiotic treatment for a pulmonary exacerbation (n=10) and healthy controls (n=10). CF patients were 7-17 years of age. Mean FEV1 in the stable CF patients was 80.4 (range 47-117%) of predicted values. FEV1 in CF patients presenting with a pulmonary exacerbation was 58 (range 36-69%) of predicted and improved by 13.5 (±2.8%) with treatment.

Results: Mean (±SEM) spermine concentration in sputum was significantly higher in stable CF than controls (1.7±0.53.99 vs. 0.22±0.5 μmol/mL, p<0.001, paired t-test), but remained significantly increased when compared to controls (p<0.001). The change in spermine concentrations during treatment for a pulmonary exacerbation correlated significantly with the
Regulation of corticosteroid binding globulin (CBG) in the inflammatory context of cystic fibrosis
Jessica Taylard1, Carine Rebeyrol 1, Dominique Debray 1, Annick Clement 1,2, Carole Lefebvre 3, Jean-Paul Magot 3, Charlotte Robroeks, Quirijn Jöbsis, Han Hendriks, Edward Dompeling.

Background: Morbidity and mortality in cystic fibrosis (CF) are mainly caused by pulmonary complications. Early recognition of an exacerbation enables early intervention in CF management. We hypothesized that lung function indices drop significantly before an exacerbation is clinically evident, and that CF exacerbations can be predicted when lung function is assessed by means of a home monitor.

Aim: To study the expression and regulation of CBG in the liver and assess its pulmonary expression in the inflammatory context of CF.

Methods: Hepatic levels of CBG:
- Biopsies from healthy donors, cirrhotic CF and non CF patients: measure of the transcripts levels of CBG and interleukin-6.
- Hepatocarcinoma derived cell-lines Hep3B and HepG2: regulation of CBG expression.

Lung levels of CBG:
- Lung biopsies; expression of CBG
- Bronchial epithelial cell lines; regulation of CBG expression

Results: We show an increase in CBG expression:
- in the liver and lung of CF patients.
- in the hepatic and lung cell lines in an inflammatory context.

GC has no effects on CBG expression in hepatic cell lines, but increases CBG levels in the lung cell lines.

Discussion: We show stimulation of the expression of CBG in the inflammatory context of CF. Comparative results from hepatic and lung cell lines enlight a different regulation of CBG expression. Overall, increase in CBG expression in CF could mean initially a decrease in GC bio-disponibility but, ultimately, an enhanced corticosteroid half life and possible prolonged effects.

Conclusions: Spermine is significantly increased in the airways of patients with CF and linked to increase arginase activity. Further studies of the role of the polyamines for CF lung disease are warranted, as they may contribute to airways obstruction and remodeling.

Regulation of corticosteroid binding globulin (CBG) in the inflammatory context of cystic fibrosis
Jessica Taylard1, Carine Rebeyrol 1, Dominique Debray 1, Annick Clement 1,2, Nicolas Chignard 1, Philippe Le Rouzic 2, 1UMR_S938, Inserm, UPMC Univ Paris 06, Paris, France; 2Pulmonary and Cardiopulmonary Medicine, Hopital Armand Trousseau, APHP, Paris, France

Background: Cystic Fibrosis (CF) is characterised by chronic lung inflammation. In CF, glucocorticoids (GC) are a widely used therapeutic tool. However, their efficiency, and the benefit/risk ratio are still discussed. In plasma, 90% of GC is bound to the chaperone protein CBG which regulates its bio-disponibility. CBG is mainly produced by the liver. Recent works enlightened the fact that, more than a simple carrier protein, CBG could also address GC specifically to the inflammation site, thereby modulating the response to GC in an inflammatory context.

Objectives: Study the expression and regulation of CBG in the liver and assess its pulmonary expression in the inflammatory context of CF.

Methods: Hepatic levels of CBG:
- Biopsies from healthy donors, cirrhotic CF and non CF patients: measure of the transcripts levels of CBG and interleukin-6.
- Hepatocarcinoma derived cell-lines Hep3B and HepG2: regulation of CBG expression.

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- Lung biopsies; expression of CBG
- Bronchial epithelial cell lines; regulation of CBG expression

Results: We show an increase in CBG expression:
- in the liver and lung of CF patients.
- in the hepatic and lung cell lines in an inflammatory context.

Conclusions: This study ascertained important indicators of exacerbation from patients and clinicians. Reflection on the results of both Delphi studies will allow comparisons to be drawn on the perspective of CF adults versus CF clinicians to identify the areas where there are differences and also the areas where there are strong agreement.

The value of lung function monitoring by means of a home monitor in patients with cystic fibrosis
Charlotte Robroeks, Quirijn Jobis, Han Hendriks, Edward Dompeling. Pneumologie, Maastricht University Medical Center, Maastricht, Netherlands

Background: Morbidity and mortality in cystic fibrosis (CF) are mainly caused by pulmonary complications. Early recognition of an exacerbation enables early intervention in CF management. We hypothesized that lung function indices drop significantly before an exacerbation is clinically evident, and, that CF exacerbations can be predicted when lung function is assessed by means of a home monitor.

Aim: To establish agreement on indicators of an exacerbation in adults with CF.

Methods: 2 parallel Delphi web surveys in 13 UK and Ireland CF centres. Delphi 1: 31 adults with CF (FEV1 <80%) with at least one exacerbation in the previous 12 months. Delphi 2: 38 CF clinicians involved in diagnosing CF exacerbations. Round 1: A list of potential indicators of exacerbations were extracted from the literature, consultation with clinicians and adults with CF and 48 statements developed. Round 2: Participants rated their level of agreement with each statement. Round 3: Currently active. Statements not reaching consensus in Round 2 were presented to participants to re-rate. Consensus of 75% agreement was applied to all statements.

Results: Round 2. Adults with CF: 21 statements reached consensus. The top three were: “More shortness of breath than usual”, “Feeling the need to do more airway clearance than usual”, “A large decrease in lung function”. Round 2, CF clinicians: 23 statements reached consensus. The top three were: “Increased sputum”, “A large decrease in lung function (>10% FEV1)”, “Increased coughing”. Of statements reaching consensus 16 were common in both groups.

Conclusions: This study ascertained important indicators of exacerbation from patients and clinicians. Reflection on the results of both Delphi studies will allow comparisons to be drawn on the perspective of CF adults versus CF clinicians to identify the areas where there are differences and also the areas where there are strong agreement.

65. Endoscopic lung volume reduction: hype or hope?

Conclusions: Single session bilateral endoscopic lung volume reduction therapy in advanced upper lobe and homogeneous emphysema using a tissue sealant

Objective(s): This open labeled multicenter study was performed to evaluate the safety and efficacy of single-session bilateral 4-site lung volume reduction therapy with the AzriSael® Emphysematous Lung Sealant System (ELS) in patients with advanced upper lobe heterogeneous (ULF) and homogeneous (Ho) emphysema.

Methods: 20 patients with advanced Ho (n=4) and ULF (n=16) emphysema received 4-site bilateral upper lobe volume reduction with ELS under conscious sedation. Outcome measures include pulmonary function tests (at 6, 12 and 24 wks), exercise capacity, symptoms, and health related quality of life (HRQL, at 12 and 24 wks).

Results: 4-site therapy was well tolerated. Procedure duration was 14-4 minutes. Average hospital length of stay was 0.9±1.3 days. There were 5 3AEs during the first 85±32 days of follow-up (5 treatment related, 1 CPDP exacerbation).

Conclusions: Bilateral single session endoscopic lung volume reduction therapy can be achieved safely using ELS in patients with advanced Ho and ULF emphysema under conscious sedation. Initial results indicate that efficacy responses are similar to those reported with surgical volume reduction, and treatment is associated with short hospital length of stay and minimal morbidity.
Background: A recent approach to bronchoscopic lung volume reduction (BLVR) in patients with advanced emphysema involves the use of a device made of self-expandable nitinol wire for the treatment of emphysema. A multicenter, single-arm cohort trial of 14 patients was performed to evaluate the feasibility, safety, and efficacy of this treatment. The primary outcomes included physical examination, imaging (CT scan to evaluate regional volumetric changes), pulmonary function tests, and quality of life assessment.

Methods: A total of 14 patients were enrolled in the study, and all patients were treated with the same procedure. The device was inserted through a flexible bronchoscope and positioned in the target lung segment. Imaging was performed before and after the procedure to assess changes in lung volume and function.

Results: All patients were successfully treated with the device. There were no procedure-related complications. One patient experienced minor hemoptysis, and another patient had a transient increase in post-procedural bronchodilator use. All patients showed improvement in pulmonary function tests and quality of life assessments at 6 months follow-up.

Conclusion: Endobronchial lung volume reduction with this device is feasible and safe, with promising clinical outcomes. Further studies are needed to confirm these results and to evaluate the long-term effects of this treatment.
Objective: To evaluate the effectiveness of the Chartis® system in predicting subjects with heterogeneous emphysema who will achieve significant (≥350mL) LVR by EVBT.

Methods: Patients with heterogeneous emphysema were enrolled. Following Chartis assessment of the targeted patients, which was determined by using HRCT, all patients were treated with Zephyr® EVBY. Primary endpoint was HRCT-measured LVR in the treated lobe at 30 days. FEV1, SGRQ and 6MWT were evaluated as secondary endpoints.

Results: To date, primary endpoint is collected for 24 patients. Primary and Secondary Endpoints for 75-80 patients are anticipated. Subgroup analyses will focus on patient selection criteria.

Conclusion: Chartis System predicts significant LVR after EVBY treatment. Results suggest that expanded patient selection criteria will enable successful treatment for a broader population of emphysema patients.

6-month follow-up in patients with advanced homogeneous emphysema treated with endobronchial lung sealant therapy

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Objective(s): Bronchoscopic lung volume reduction therapy using endobronchial valves (Scurfa F et al., NEJM, 2010;363) and coils (Herth FJ et al. Therap Adv Respir Dis, 2010;4) has shown limited efficacy in patients with advanced homogeneous emphysema (sAHoE). This study summarizes results to AeriSeal® Emphysematous Lung Sealant (ELS) therapy in patients with sAHoE out to 6 months.

Methods: Patients with sAHoE and scintigraphy scans showing reduced perfusion to the upper lung zones (n=12) were included in this study, which was performed at 8 investigational centers in Europe and Israel. All patients received initial 2-site upper lobe bronchoscopic ELS therapy; approximately 2/3 received a second treatment at 2 additional sites in the contralateral lung. Follow-up was performed at 3 and 6 months post treatment.

Results: Upper lobe ELS therapy in this cohort of sAHoE patients (8 male, age 64±7 yrs) was well tolerated, and was associated with improvements in pulmonary function, functional capacity, and quality of life. Three (3) and 6 month changes in FEV1 (+12.6 ±13.1%), FVC (+9.4 ±13.2%); FVC (+9.9 ±10.1%), RV/TLC ratio (−3.6 ±3.8%), sFEV1 (−0.4 ±0.0%) and 6MWT (+15.4±4.5m; +16.6±4.7m), and SGRQ (−7.9 ±7.6); −13.3 ±23.0) were observed. MCI improvements in spirometry (>12% improvement in FEV1 and/or FVC) were observed in 50% of patients at both time points.

Conclusions: ELS therapy produces durable improvements in pulmonary function and quality of life in patients with AHSIE, and represents a new therapeutic option for patients with homogeneous emphysema who remain symptomatic despite maximal medical therapy.

Efficiency of the endo-bronchial volum reduction treatment for severe heterogeneous emphysema

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Background: Patients with advanced chronic obstructive pulmonary disease (COPD) have limited treatment options. Exercise capacity and health related quality of life (HRQoL) of the patients are affected by the progress of respiratory failure. Volum reduction surgery is reported to be effective for selected patients. But there is a high risk for the surgery of these patients.

Methods: To study the safety and effectiveness of the EBVRT for heterogeneous emphysema.

Result: EBVRT were applied to 21 patients. Most of the patients were male (66.6%). Valves were placed into upper lobe (n=15), lower lobes (n=5) and middle lobe (n=1). There were no procedure-related deaths. Only one patient with ischemic heart disease was died at the 3rd month. Device related complication was occurred in two patients; one patient was intubated and the other patient’s valve was occluded and worked inversely. Functional capacity was improved in 715% (n=15) of the patients but only 66% (n=10) of these patients were feeling and doing better. In these patients mean 10mmHG increase of PaO2 and mean 4.5mmHG decrease of PaCO2 were observed at 3rd month. HRQoL were improved in 48% (n=10) of the patients. However, pulmonary functions, 6 minute walking distance were not significantly changed.

Conclusion: Although FEV1, 6 minute walking distance were not changed, PaO2, functional status and HRQoL improvement were observed with EBVRT of advanced emphysema patients. EBVRT is a new method with acceptable safety for the patients with severe COPD.

Late-breaking abstract: Impaired carbon monoxide diffusion capacity is the strongest predictor of exercise intolerance, even in moderate COPD

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Background: Exercise intolerance is the hallmark of COPD and FEV1 is the traditional method used to define the severity of COPD. However there is a dissociation between FEV1 and exercise capacity in a large proportion of subjects with COPD. Therefore it is of interest to investigate if other lung function parameters are having an additive, predictive value of exercise capacity (EC) and if this differs according to the COPD stages.

Methods: Spirometry, measurements of lung volumes and diffusing capacity for carbon monoxide (DLCO) were performed in 88 patients with COPD GOLD stages 1-IV. EC was determined by symptom-limited incremental cycle ergometer test.

Results: DLCO, FEV1 and inspiratory capacity (IC) were found to be the best predictors of EC in a stepwise regression analysis and explain 72% of EC. These lung function parameters explained 71% of EC in GOLD II, 69% in GOLD III and 32% in GOLD IV. DLCO alone was the best predictor of exercise capacity in GOLD II and IV (Table).

Discussions: Additive information regarding COPD patients’ exercise capacity is obtained by measuring diffusing capacity and inspiratory capacity. DLCO was the strongest predictor of exercise capacity in all subjects and the best individual predictor in patients with GOLD stage II. This suggests that clinically monitoring with measurements of diffusing capacity may be beneficial even in patients with moderate disease severity.

ACE gene polymorphisms, COPD exercise tolerance and response to acute oxygen

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Introduction: Recent studies have shown that polymorphisms of the angiotensin-converting enzyme (ACE) gene are closely associated with pulmonary disorders. The aim of this study was 1) to investigate the impact of ACE gene polymorphism on exercise tolerance 2) to determine whether a relationship exists between oxygen responses and differential genotype (DD, DI or II).

Methodology: Twenty-four COPD patients [FEV1=51±2.4%pred] exhibiting exercise-induced desaturation performed endurance exercise at 60% of their maximal workload in two randomised conditions: normoxia and hyperoxia. ACE genotype was determined for each patient. Endurance time (Tlim), dyspnoea, cardiac output (CO) and arterio-venous difference in oxygen (AVD) were compared.

Results: In normoxia, Tlim was greater for DI than DD (1168 vs 541s; p<0.05). Oxygen supply improved performance in both groups, but DI again exhibited better endurance than DD (1313 vs 1332s; p=0.01). This better exercise capacity in DI was associated with a greater AVE and decreased CO for comparable oxygen uptake. Although O2 significantly increased Tlim in two-thirds of patients (R=+) and significantly decreased it in about one-third (R=−). R=+ and R− proportion was comparable in the two genotype groups (ch2=0.52, p=0.66).

Conclusion: This study showed that DI-allele was associated with better endurance performance. Although DD and DI increased performance with oxygen, responses were associated with differential consequences on cardiovascular and peripheral muscle adaptations. However, ACE polymorphism could not be related to positive or negative oxygen responses.

66. Altered mechanisms during exercise in disease

Late-breaking abstract: Impaired carbon monoxide diffusion capacity is the strongest predictor of exercise intolerance, even in moderate COPD

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ACE gene polymorphisms, COPD exercise tolerance and response to acute oxygen

Nelly Heraud1, Christian Préfaut2, Jacques Desplas1, Alain Varray3, Clinique du Souffle, Fonteville, Osexe, France; 2Physiologie et Medecine Experimentale du Cerveau et des Muscles - INSERM U 1046, CHU de Montpellier, Montpellier, France; 3EA 2991 - Laboratoire Mouvement a Health ou Mouvement et Santé, Université Montpellier 1, Montpellier, France

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Conclusion: This study showed that DI-allele was associated with better endurance performance. Although DD and DI increased performance with oxygen, responses were associated with differential consequences on cardiovascular and peripheral muscle adaptations. However, ACE polymorphism could not be related to positive or negative oxygen responses.
378 Influence of abdominal volume regulation on chest wall hyperinflation during constant work rate exercise in patients with COPD
Luciana Takara, Marco Nunes, Thulio Cunha, Fabio Queiroga, Miguel Rodrigues, Ethane Meda, Mayron Oliveira, Gaspar Chiappa, Luiz Eduardo Nery, J. Alberto Nedert. Respiratory Div., Federal Univ. of Sao Paulo, Sao Paulo, Brazil

It has been recently reported that some patients with chronic obstructive pulmonary disease (COPD) may actively recruit the expiratory abdominal (AB) muscles in order to counteract the related dynamic hyperinflation. However, whether this strategy is universally efficacious in counterbalancing the potential increases in rib cage (RC) volumes thereby promoting a net deflating effect on chest wall (CW) is unknown. Thirteen males with COPD (FEV1=43.8±9.5%) performed a constant work rate cardiopulmonary exercise test (75% max) to the limit of tolerance (Tlim) on a cycle ergometer. Breath-by-breath ventilatory kinematics was continuously monitored by optoelectronic plethysmography (BTS, Italy). End-expiratory volume of RC (EEVRC) and EEV CW significantly increased from rest to Tlim in 17 patients. EEV CW remained stable in 9 of them ("non-recruiters/hyperinflators"); in contrast, it decreased slightly in 7 "recruiter/hyperinflators" thereby lessening CW hyperinflation. EEV RC remained stable and EEV AB decreased sharply in the remaining 13 "recruiter_non-hyperinflators". "Recruiter/hyperinflators" showed higher dyspnoea scores and the worst exercise capacity (~80% lower than the "recruiter_non-hyperinflators") (p<0.05). In conclusion, CW deflation secondary to extensive AB recruitment was restricted to COPD patients showing no evidences of RC hyperinflation. On the other hand, pronounced increases in RC volumes were associated with milder degrees of AB recruitment. Although this avoided more severe CW hyperinflation, it was related to increased breathlessness and poor exercise tolerance. Supported by: FAPESP and CNPq, Brazil.

379 Effect of heliox breathing on locomotor and respiratory muscle oxygen delivery during exercise in COPD patients with or without dynamic hyperinflation
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Background: Dynamic hyperinflation and large intrathoracic pressure swings in ducd exercise in COPD. Heliox breathing reduces the degree of dynamic hyperinflation thereby improving peripheral muscle oxygen delivery. Whether this effect also applies to patients who do not hyperinflate during exercise, is unknown.

Methods: 17 COPD patients (n=8 hyperinflators [FEV1=37±4% pred] and n=9 non-hyperinflators [FEV1=48±4% pred]) performed two constant-load exercise tests to the limit of tolerance in air and whilst breathing heliox.

Results: The improvement in exercise tolerance by heliox was not different between hyperinflators and non-hyperinflators (by 3.8±1.9 and 4.2±2.0 min, respectively). This is probably due to the finding that systemic oxygen delivery significantly improved in both hyperinflators (from 1.48±0.10 to 1.70±0.11 L/min) and non-hyperinflators (from 1.68±0.12 to 1.93±0.15 L/min); however, the mechanism of improvement was different as heliox improved cardiac output in both hyperinflators (from 9.3±0.5 to 10.4±0.5 l/min) whilst arterial oxygen content increased only in hyperinflators (from 160±3 to 177±4 ml/dlO2). Nonetheless, quadriiceps and intercostal muscle oxygen delivery (measured by NIRS+ICG with arterial sampling) improved significantly and by the same magnitude in both hyperinflators (by 16.6±7.4 and 4.0±1.1 mlO2/min/100g, respectively) and non-hyperinflators (by 17.6±8.2 and 4.5±1.2 mlO2/min/100g, respectively).

Conclusion: Heliox improves peripheral and respiratory muscle oxygen delivery in all COPD patients regardless of the occurrence of exercise-induced dynamic hyperinflation.

380 Effects of oxygen supplementation on cerebral oxygenation during progressive exercise in patients with COPD and healthy controls
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The rate of change (Δ) in cerebral oxygenation (CO2) during exercise is modulated by cerebral blood flow and arterial O2 content (CaO2). It is currently unclear whether ΔCO2 would (i) be impaired during exercise in patients with chronic obstructive pulmonary disease (COPD) who are not overtly hypoxaemic and (ii) improve with hyperoxia (HiO2, FIO2=0.4) in these patients. Twenty non-hypcapnic males with COPD (FEV1=47±2%±11.5% predicted) and 9 age- and gender-matched controls performed a sub-maximal incremental exercise test under HiO2 and normoxia (NOX). ΔCO2 was determined by near infrared spectroscopy (fold-changes in HbO2 and cardiac output (QT) by impedance cardiography. A significant drop in SpO2 was found in 8/20 patients (peak SpO2=86±2% vs. 96±2% for “desaturators” (DESAT) and “non-desaturators” (NONDESAT), respectively. In NOX, ΔCO2 was lower in DESAT versus NONDESAT and controls; in contrast, arterial oxygen pressure (MAP) was higher in the former group (p<0.05). Increases in SpO2 with HiO2 were particularly pronounced in DESAT (86±2 vs. 99±1%); interestingly, no significant improvement in COPD was found only in this group (0.52±0.20 vs. 2.09±0.42; p<0.01). There was no significant effect of HiO2 on QT in control and COPD groups; MAP; however, decreased in DESAT (p<0.05). ΔCO2 is impaired in COPD patients with CTPH during progressive exercise even if they are not entitled to long-term O2 therapy. O2 supplementation (FIO2=0.4) is able to correct for these abnormalities, an effect that was related to enhanced CaO2 rather than improved cerebral haemodynamics. Supported by: CNPq and FAPESP, Brazil.

381 Locomotor muscle afferents contribute to ventilatory control during exercise in heart failure patients
Thomas Olson1, Michael Joyner1, John Eisenach2, Timothy Curry2, Bruce Johnson3. 1Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States; 2Anesthesiology, Mayo Clinic, Rochester, MN, United States

Background: Reduced ventilatory efficiency is a hallmark of heart failure (HF) and is linked to disease severity and worse prognosis. Mechanisms responsible for altered ventilatory efficiency remain poorly understood but may include neurologic feedback from locomotor muscles. This study was designed to determine the impact of blocking locomotor muscle afferent feedback on ventilation (VE) during exercise in HF patients.

Methods: 5 HF patients with reduced systolic function (age=60±11 yrs, hHF/EV1=31±6 l/min, w=94±7 kg, exercise at 75% peak work) underwent an incremental exercise test on a cycle ergometer. Breath-by-breath measures included VE, breathing frequency (fb), tidal volume (VT), end-tidal carbon dioxide (PaCO2), and carbon dioxide production (VCO2). Central chemoreceptor sensitivity was also measured via CO2 rebreathe.

Results: At end exercise, there was no difference in VO2 (1.4±0.2 vs 1.4±0.2 L/min, p=0.43), whereas VE was reduced with RBN (48.0±6.5 vs 41.8±6.0 l/min, p<0.05) through a reduction in fb (27.2±5.2 vs 23.9±4.2 breaths/min, p<0.01) with no change in VE (1.8±0.2 vs 1.8±0.2 L/min, p=0.81). Additionally, the V/PaCO2 ratio was reduced with RBN (33.2±3.5 vs 28.2±2.8, p<0.05). After exercise, there was no difference between the conditions for chemoreceptor sensitivity (V/PaCO2 slope: 2.4±0.9 vs 2.4±0.9, p=0.80).

Conclusion: In HF patients, blocking afferent neural feedback from the locomotor muscles during exercise reduces VE and improves ventilatory efficiency. Funded by NIH/NCC grant KL2-RR024151.

382 Comparing cardiopulmonary responses to incremental exercise in patients with chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension
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Patients with chronic thromboembolic pulmonary hypertension (CTPH) are more likely to develop proximal locomotor lesions than those with idiopathic pulmonary arterial hypertension (PAH). Therefore, CTPH might present with poorer right ventricle pulmonary vascular coupling, worse ventilation-perfusion matching and, lower maximal exercise capacity compared to IPAH. We comparatively evaluated 26 patients with CTPH and 14 with IPAH who underwent a symptom-limited incremental exercise test on a cycle ergometer. Haemodynamic variables (systolic volume [SV] and cardiac index [CI]) were measured by impedance cardiography. Baseline characteristics were similar in CTPH and IPAH (age=48±4 vs 52±5 yrs; p=0.5). However, CTPH patients had higher AV El/AV CO2 (75±26 vs 52±17; p<0.05), lower end-tidal CO2 pressure at the anaerobic threshold (21±4 vs 28±6 mmHg; p=0.05) and greater oxyhaemoglobin desaturation (peak SpO2, 88±7 vs 93±6%; p<0.05). In conclusion, patients with CTPH had higher sub-maximal ventilatory response to progressive exercise compared to those with IPAH. Although this difference did not impact upon peak exercise capacity, it indicates that CTPH led to more extensive pulmonary gas exchange abnormalities despite similar resting and exercise haemodynamic impairment.

383 Do respiratory mechanics abnormalities contribute to exertional dyspnoea in patients with pulmonary hypertension?
Peranatov Lavenets1, Giles Garci2,3, Fabio Nicolas-Jalwan1, Christian Strat1,2, Xavier Jais 1,3, Laurent Savale2,3, David Montani2,3, Olivier Sitbon2,3, Gérald Simonneau2,3, Marc Humbert1,2, Thomas Similowski1.

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GIP was associated with (p < 0.05) more neutropenia, thrombocytopenia, vomiting, while more cardiovascularity, diarreha and peripheral neuropathy was observed with DP and epicaplopathy with IG.

Conclusion: In this large phase III trial, a non-platinum CT regimen (ifosfamide-gemcitabine) had similar activity to cisplatin-based CT in terms of survival, PFS and response rates with a favourable toxicity profile.

386 Gemcitabine sensitizes lung cancer cells to Fas/Fas ligand system-mediated killing
Liborja Siena, Elisabetta Pace, Maria Ferraro, Caterina Di Sano, Mario Melis, Mirella Profita, Mark Gjomarkaj. Institute of Biomedicine and Molecular Immunology (IBIM), National Research Council (CNR), Palermo, Italy

Gemcitabine (GEM) is an agent commonly used in the treatment of non small cell lung cancer (NSCLC). GEM induces apoptosis in NSCLC cells indirectly by increasing functionally active Fas expression. To further explore the mechanisms involved in the activation by GEM of apoptosis extrinsic pathway in lung cancer cells, we evaluated the ability of GEM to up-regulate the expression of Fas, in NSCLC H292 (mucocoeplar cell carcinoma) line and to increase the sensitivity of these cells to Fas-mediated killing of cytotoxic lymphocytes. Cells were cultured with and without GEM (0.05 μM for 72, 48, 72 and 96 hrs) respectively and protein were evaluated by real-time PCR, and by western blot and flow cytometry, respectively. Apoptosis of cells expressing Fasl was evaluated by flow cytometry. Cytotoxicity of LAK and malignant pleural fluid (PF) lymphocytes against H292 cells was analyzed in presence of GEM, by flow cytometry-based assay. Expression of FasL, mRNA and protein in H292 cells after incubation with GEM was increased at all time-points and this increase was higher after 72 hrs. Accordingly, the percentage of apoptotic H292 cells expressing Fasl was higher after 72 hrs. Cytotoxicity of LAK and PF lymphocytes was significantly increased after incubation of H292 cells with GEM and was partially inhibited by neutralizing anti-Fas antibody.

These data demonstrate that: 1) GEM induces an up-regulation of FasL in NSCLC cells triggering cell apoptosis via an autocrine/paracrine loop; 2) GEM is able to increase the sensitivity of NSCLC cells to cytotoxic activity of LAK and PF lymphocytes by activation of Fas-Fasl signalling system.

387 Non-small cell lung cancer treatment by inhalation of Erbitux and gemcitabine in murine model
Cathda Schwarz1, Ofer Merinisky2, Alex Sturr1. 1Pathology Dept., Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Our study tested the efficacy of chemotherapy delivered by inhalation in murine model of lung cancer.

Methods: Mouse models of human (H226) and murine (3LL) non-small cell lung cancer (NSCLC) were used. Cultivated human NSCLC cells were inoculated orthotopically into the lung (H226) or intravenously (3LL) producing advanced disseminated lung cancer. Aerosols were delivered daily from day 5 to day 30 (after tumor cell inoculation) using an ultrasonic nebulizer in a cage specifically constructed to in total dosage 30mg/kg (Erbitux) and 0.5mg/kg (Gem). The effect of nebulization on Erbitux was assessed in terms of its affinity for membrane EGFr (using ELISA), inhibition of cell growth (XTT assay) and inhibition of EGFR phosphorylation (by immunoprecipitation).

Results: Significant inhibition of tumor growth by Erbitux alone or in combination with Gem was observed. Inhalation of Erbitux in 3LL resulted in 50% reduction of lung weights and number of tumor nodules. Nebulized Gem demonstrated 80% decrease in the lung weight and tumor foci whereas combination therapy resulted in complete disappearance of tumor masses. Inhalation in H226 with Erbitux demonstrated 10% reduction of lung weight, 40% reduction with Gem and 50% with combination therapy. Inhalations were well tolerated without toxicity to lungs, kidney, colon, skin, liver or spleen.

Conclusions: We demonstrated the efficacy of the aerosol treatment by Erbitux and Gem in animal model of NSCLC without any pulmonary toxicity. The study demonstrated therapeutic perspective of aerosol delivery of Erbitux/Gem in the treatment of patients with advanced disseminated lung cancer.

388 Late-breaking abstract: Relationship of aquaporin 1, 3 and 5 expression in lung cancer cells to cellular differentiation, invasive growth and metastatic potential
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An oncogenic capacity of aquaporins (AQPs), transmembrane channels for water, was recently proposed. This study seeks to elucidate the involvement of AQPI, 3 and 5 in the development and progression of lung cancer. Expression analyses of AQPI, 3 and 5 by immunohistochemistry, western blot and real time-PCR in 160 lung cancers showed that AQPI, 3 and 5 were expressed in 71, 40 and 56%, of lung cancers, respectively. AQPI expressing frequencies were frequent in adenosquamous carcinomas (ADCs), whereas in all healthy subjects IC decreased with 0.2L/min, dyspnoea intensity (by Borg scale) were assessed throughout CPET. In 70% of PH patients (n=14), IC decreased progressively throughout CPET by 0.3L/min on average (dynamic hyperinflation), whereas in all healthy subjects IC increased by 0.2L/min. Dyspnoea intensity and minute ventilation (VE) were greater in PH patients at any stage of CPET compared with healthy controls: at standardized work rate of 60watts, dyspnoea rating and V'E were 5 Borg units and 45L/min respectively in PH patients compared with 1 Borg unit and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with greater dyspnoea (by 4 Borg units) and hypoxic apnea (by 2 Borg units and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with greater dyspnoea (by 4 Borg units) and hypoxic apnea (by 2 Borg units and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with greater dyspnoea (by 4 Borg units) and hypoxic apnea (by 2 Borg units and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with greater dyspnoea (by 4 Borg units) and hypoxic apnea (by 2 Borg units and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with great...
Carboplatin-paclitaxel alone or with bevacizumab in stage III-IV lung cells to gefitinib. Thus, FoxM1 could be used as a therapeutic target of gefitinib. These data suggest that FoxM1 confers the resistance of lung cancer SPC-A-1 cells with gefitinib treatment. Moreover, the increased protein level of and 0.1 \textsuperscript{46\%}, 54\% in H292 cells with 10 \textmu M and 1

The mRNA levels of FoxM1 in SPC-A-1 cells at 24, 48 and 72 hours cell survival and apoptosis in N-FoxM1 and vehicle groups. (N-FoxM1 group) was established. MTT assay and FCM were used to detect the cell survival and apoptosis in N-FoxM1 and vehicle groups. Results: The mRNA levels of FoxM1 in SPC-A-1 cells at 24, 48 and 72 hours after recombination of gefitinib increased by 38\%, 53\%, 72\%, while reduced by 23\%, 46\%, 54\% in H292 cells with 10 \textmu M and 1 \textmu M of gefitinib. The survival rates of N-FoxM1 and vehicle groups with incubation of 1, 6, 24, 48 and 72 hours. After preoperative treatment partial response of tumor was achieved in 16\% of cases and patients underwent surgery with radical intent. There was no post PDT complication. 14 operations were R0, 2 – R1. No major postoperative complications noted except cardiac arrhythmia in 3 patients (19\%). Average period of follow-up was 16 months (4 to 30 months), all patients are alive without any signs of recurrence. Conclusion: The first experience of the combined treatment including intraoperative PDT for locally advanced NSCLC demonstrates safety and effectiveness. Additional studies are needed to proof the value of intraoperative PDT.

68. Multidrug-resistant tuberculosis

The 2011 update of the World Health Organization guidelines for the programmatic management of drug-resistant tuberculosis

Methods: WHO commissioned systematic reviews of evidence, including meta-analysis and modeling studies, to summarize evidence on priority questions regarding case finding, treatment regimens for multidrug-resistant TB (MDR-TB), monitoring of response to MDR-TB treatment and models of care. The quality of evidence assembled varied from low to very low. A multidisciplinary expert panel used the GRADE approach to develop recommendations based on best available evidence.

Findings: The recommendations encourage the wider use of rapid drug-susceptibility testing with molecular techniques to detect rifampicin resistance and treat patients adequately. The use of culture remains important for the early detection of failure during MDR-TB treatment. The guidelines provide recommendations about the early use of anti-retroviral agents for TB patients with HIV who are on second-line TB drug regimens. Systems that primarily employ ambulatory stages of care to manage MDR-TB patients are recommended over others mainly on hospitalization.
Conclusion: Practitioners and decision makers involved in MDR-TB care should be guided in their work by these updated recommendations. Additional research is necessary to improve the quality of existing evidence, particularly on regimen composition and duration of treatment.

394 Treatment outcomes for multidrug-resistant tuberculosis (MDR-TB) patients in Africa

Valeria Crudu1, Victor Botnaru1, Ecaterina Stratan 1, Olga Golisceva1, Valeriu Crudu1, Victor Botnaru1, Ecaterina Stratan 1, Olga Golisceva1, Daniela Homorodean, Iuliana Husar, Cristian Popa, Felicia Cojocaru, Elmira Braim. Reference Laboratory, Clinical Hospital of Pneumology, Cluj-Napoca, Romania Service de Pneumologie, Centre Hospitalier de Dieppe, Dieppe, France Pneumology, Pneumology Institute Marius Nasta, Bucharest, Romania

Introduction: As countries in Africa scale up their treatment of multidrug-resistant tuberculosis (MDR-TB) patients, it is important to monitor the results of treatment efforts.

Methods: In 2010, as part of its global TB surveillance activities, the World Health Organization gathered information on treatment outcome cohorts of MDR-TB patients starting treatment in 2007. The delay allowed programmes time to recover data for patients whose treatment commonly lasts two years or more.

Results: Seventeen of the 46 countries in the African region reported treatment outcomes for an aggregate of 4532 MDR-TB cases, mostly from South Africa (3815). Thirteen of these countries had notified a total of 8234 MDR-TB cases in 2007 (4 countries had no data), and outcome cohorts varied in size between 20% and >100% of cases originally notified. Outcome reports were incomplete with five national cohorts having no information on >20% of the patients treated. Treatment success ranged between countries from 14% to 100% of patients (median: 60%) and deaths from 0% to 57% (median: 14%). Defaults were more frequently reported (12 countries; median 9%) than failures (5 countries; median 0%).

Conclusions: Coverage and success in the African cohorts are comparable with other regions in the world. Reports on enrolment of MDR-TB patients on treatment and their outcomes are incomplete in many countries even when compared to other regions by the countries capacity for scaling up care and ineffective reporting. Treatment success for MDR-TB patients remains low as a result of a high risk of dying, of failed treatment or of interruption of prescribed treatment.

395 Increasing TB drug resistance in Moldova during the 2006-2010

Valeriu Crudu1, Victor Botnaru1, Ecaterina Stratan 1, Olga Golisceva1, Valeriu Crudu1, Victor Botnaru1, Ecaterina Stratan 1, Olga Golisceva1, Valeriu Crudu1, Victor Botnaru1, Ecaterina Stratan 1, Olga Golisceva1, Daniela Homorodean, Iuliana Husar, Cristian Popa, Felicia Cojocaru, Elmira Braim. Reference Laboratory, Clinical Hospital of Pneumology, Cluj-Napoca, Romania Service de Pneumologie, Centre Hospitalier de Dieppe, Dieppe, France Pneumology, Pneumology Institute Marius Nasta, Bucharest, Romania

Background: The emergence of drug-resistance (DR) hampers tuberculosis (TB) control. The level of primary DR, particularly multidrug resistance (MDR) is one of the main causes of ineffective treatment of new TB cases. The aim of the study was to estimate the trends of TB DR in Moldova during the last 5 years.

Materials and methods: Retrospectively analysis of 11,193 cards of drug sensitivity tests performed in the National TB Reference Laboratory and three Regional TB Reference Laboratories during 2006-2010. DST was performed on L-J media using absolute concentration method and on liquid media (MGIT960) in laboratories with controlled quality (concordance with reference laboratory >95%). The last two years were implement the Hain method for rapid diagnosis of MDR TB.

Results: From all examined patients, 5241 (47,2%) were new TB cases tested for 1st-line drugs was conducted on all isolates; DST for selected 2nd-line drugs was performed at the Stockholm Supranational Reference Laboratory. External quality assessment of DST was performed at the Stockholm Supranational Reference Laboratory.

Conclusion: The level of primary DR has been increasing from 42.9% to 49.5% yearly. The first XDR-TB case has been reported in 2006. The level of secondary DR also has been increased from 70.5% to 80.2% respectively. In 28% of subjects no DST was performed before the survey. The most frequent MDR-TB cases were chronics (285-37.7%), followed by relapses (191-25.5%), new cases (103-13.4%), retreatments after failure (92-12.2%) and retreatments after default (80-10.6%). In 7 cases (0.9%) the category by treatment history was unknown. Out of 388 HIV tested MDR-TB patients 10 (2.6%) were positive.

Conclusions: The XDR-TB rate among MDR-TB cases in Romania is 11.2%. In order to early detect drug-resistant cases it’s necessary to test all strains from retreated TB cases and from new cases with high risk for MDR.

396 Drug-resistant tuberculosis in Belarus: Results of the first representative survey

Alena Skrakhina1, Aksana Zalutskaya1, Sahalychtch Evgvni, Andrei Astrazko2, Wayne Van Gemert3, Sven Hoffner2, Valeraniu Rusovich2, Matze Zignol2, Henadz Hurevich1, 1MDR Tuberculosis Clinic, Hospital General de Tijuana, Tijuana, Baja California, Mexico; 2TB and Refugee Health Branch, San Diego County Health and Human Services Agency, San Diego, CA, United States; 3Director, Facultad de Medicina, Universidad Autonoma de Baja California, Mexico; 4MDR Tuberculosis Clinic, Hospital General de Tijuana, Tijuana, Baja California, Mexico

Background: Multidrug resistant tuberculosis (MDR-TB) is expensive to diagnose and treat, and requires a high degree of expertise by the laboratory and medical team, resources that may be scarce in regions with the highest rates of MDR-TB. Baja California, a Mexican state that shares the international border with California, United States (USA) has the highest rate of tuberculosis in the country.

Methods: A binational consortium constituted by USA and Mexico partners started a program dedicated to the diagnosis and treatment of MDR-TB in the region. All regions were involved in the program and diagnosis was done through the national laboratory network. All the patients who were diagnosed with drug resistant tuberculosis were treated with the national program with guidelines provided by the World Health Organization (WHO). The program was supported with funding from the United States Agency for International Development (USAID) and the program was supported by the Drug Repatriation Program (DRP). A binational laboratory network was created to support the program. The network included the Regional Reference Laboratory, the National Reference Laboratory, and the State Reference Laboratory in Baja California.

Results: From June 2006 through December 2010 forty patients started treatment. The lapse between their initial diagnosis and the referral to the program was 43.6 months; they had received 2.15 treatment regimens in the past. Their strains were resistant to 4.15 drugs: 2 patients (5.1%) had an XDR-TB strain. All patients converted their culture on treatment, on average after 4.0 months.
Nineteen patients (47.5%) have been discharged as cured (mean follow-up after discharge 6.8 months), 3 patients died (7.5%) and one patient abandoned (2.5%).

Conclusion: Highly resistant cases can be cured under a well-organized, outpatient program. In this consortium the USA partner introduced program elements that have been gradually integrated into the state TB program. After 5 years, the consortium continues to fine-tune sustainable interventions and provides quality control.

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Tuberculosis in household contacts of multidrug-resistant tuberculosis patients
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Setting: The burden of tuberculosis disease amongst household contacts of multidrug-resistant tuberculosis patients is poorly understood and might represent a target for transmission-interrupting interventions.

Design: This retrospective cohort study conducted in Lima from June to September 2008, estimated the incidence of tuberculous disease among household contacts of multidrug-resistant tuberculosis patients in 358 households.

Results: 108 (5%) of 2121 household contacts in 80 households (22% of households) developed tuberculous disease during the study, equating to an incidence rate of 2360 per 100,000 contact follow-up years for each of the first 3 years after exposure. Drug susceptibility tests were available on 50 diseased contacts of whom 36 (72%) had multidrug-resistant tuberculosis. Forty-two pairs of index-contact drug susceptibility tests were available amongst which the contact had an identical or less resistant phenotype than the index case in 27 pairs. Multivariate clustered Cox regression demonstrated that contacts with a previous history of tuberculosis disease (Hazard Ratio 15.0, P<0.001) and with associated (non-HIV) comorbidities (Hazard Ratio 7.8, P<0.001) were significantly more likely to develop tuberculosis.

Conclusion: The high percentage of diseased household contacts highlights an opportunity for household level interventions to prevent transmission, whether or not these subsequent cases were all attributable to the index case.

Late-breaking abstract: Factors associated with medication adherence in patients with COPD
Ilkay Koca Kalinkad, A Fusun Kalkapikolu | Department of Pulmonary Medicine, Kirikkale University Faculty of Medicine, Kirikkale, Turkey

Background: Only about 50% of patients with COPD, 4th leading cause of death, adhere to prescribed regimen. Non-adherence is one of the most important obstacles in achieving optimized clinical-outcome. The purpose of this study is to identify the clinical predictors of medication adherence.

Method: 51 patients with prescribed regular medication due to COPD, were included in the study. Sociodemographic (age, sex, educational level, BMI, comorbidity, number of additional drugs), COPD-related (smoking habits, duration of disease, MRC-dyspnea-score, treatment, exacerbations) and spirometry variables were recorded. Personality traits (Eysenck Personality Questionnaire), self report of medication adherence (MARS) and health related quality of life (SF-36) were evaluated.

Results: The mean-age was 63±9.2 years, 48 (94%) were male, 68.6% had low educational level (<8 years), mean FEV1 was 40.4±20.9%, 58% had MRC-score of <3, exacerbations-per-year was 2.2±1.9. 22 of the patients had comorbidity diseases with mean number of 3.7±2.4 additional drugs and weren't correlated with MARS. Mean MARS was 20.6±4.1 and 33.3% were nonadherent. MARS was correlated neither with personality traits nor SF-36. MARS was significantly higher in patients who reported themselves as regular-medication-user and benefited from therapy (p=0.001, p=0.03 respectively). Patients taking nebulizer treatment found to have significantly lower MARS than patients taking LABA (p=0.001), which was found to be intentional.

Conclusions: We found that, neither the sociodemographic variables, personality traits nor the disease severity, but the routinization of recommended treatment and faith in the treatment are critical for optimal medication adherence in patients with COPD

Diagnosis and predictors of COPD exacerbation

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Admission cTnI was “undetectable” (U, 0.02-0.05 μg/L) in 59%, “measurable” (M, 0.02-0.05 μg/L) in 35% and “elevated” (E, >0.05 μg/L) in 26% of patients. The table shows mortality at various timepoints. The classic triad of symptoms was reported in 40.2% of the pts. BGA on admission was measured in 74% and chest-x-ray was performed in 86.6% of the pts.

Conclusion: These results help us characterise unselected COPD exacerbations as seen in clinical practice. Whilst most are admitted with dyspnea, only a minority shows the classical triad of symptoms. The high number of current smokers and the low availability of spirometry suggest to improve implementation of evidence based interventions. The severe stage of COPD in the majority of hospital admissions would justify BGA and x-ray in all patients.

Any detectable admission cardiac troponin I level is associated with increased risk of early death following COPD exacerbations
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Background: Elevated cardiac troponin I (cTnI) levels during COPD exacerbations predict long-term mortality (COPD 2009:6:155-61). The times at which these deaths occur is unknown. We used a time-to-event approach to further characterise the prognostic significance of this biomarker.

Method: 237 COPD patients (127 male, 73±11yrs) admitted with exacerbations between July 2008-9, and with a measured cTnI within 24h of admission were retrospectively identified. Clinical information was retrieved from the electronic patient record.

Results: Admission cTnI was “undetectable” (U, <0.02 μg/L) in 15%, “measurable” (M, 0.02-0.05 μg/L) in 35% and “elevated” (E, >0.05 μg/L) in 26% of patients. The table shows mortality at various timepoints. Figure 1 illustrates survival post-admission by initial cTnI level.

Figure 1. Mean values from 13 European countries.

The classical triad of symptoms was reported in 40.2% of the pts. BGA on admission was measured in 74% and chest-x-ray was performed in 86.6% of the pts.
Days post-admission 

<table>
<thead>
<tr>
<th>Days post-admission</th>
<th>Mortality* (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>0-30</td>
<td>U</td>
<td>M</td>
</tr>
<tr>
<td>0-30</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>30-360</td>
<td>65</td>
<td>25</td>
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<td>360-545</td>
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*Non-cumulative.

Figure 1

On Cox regression, cTnI level predicted survival (p<0.003) independently of inflammatory markers, haemoglobin, creatinine or cancer.

Conclusions: Any detectable cTnI is independently associated with increased post-exacerbation mortality, with increasing risk at higher concentrations. Excess deaths in patients with detectable cTnI occur in the first 30 days post-admission. Elucidating underlying mechanisms of cTnI rise may identify new opportunities to improve outcomes following COPD exacerbations.

402 Value of prothrombin fragments F1+2 in the diagnosis of pulmonary embolism in patients hospitalized due to COPD exacerbation

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Background: One of four COPD patients who require hospitalization for an acute exacerbation may have pulmonary embolism. Normal D-dimer is now considered to be safe enough for ruling out thromboembolism in patients with a low pre-test probability. However, 9% of patients with AECOPD with low clinical provability may still have PE, and D-dimer is normal only in minority of patients with AECOPD. The combination of D-Dimer testing with another markers of thrombosis may improve the diagnostic efficiency.

Aim: To assess the usefulness of F1+2 in the diagnosis of PE in hospitalized patients with exacerbation of COPD, and whether assay of F1+2 may have an additional value in the subgroup of patients with an abnormal D-dimer. To determine the sensitivity, specificity, NPV of F1+2 at various cut-off values.

Methods: Blood samples for F1+2 and D-dimer were obtained and CT pulmonary angiography was performed in 49 patients hospitalized due to AECOPD.

Results: Prevalence of PE was 18.37%. Patients with proved pulmonary embolism had higher values of F1+2 380 pmol/l (95% CI 235.5 - 523.7) than in patients with high D-dimer level in whom PE was not confirmed: 204 pmol/l (95% CI 140.2 - 278.6, p< 0.0042). At cutoff levels for F1+2 180 pmol/l, or lower the sensitivity was 100%, and negative predicted value -1.0. Taking a normal F1+2 level (cut-off 180) into account in the subgroup of patients with an abnormal D-dimer added significant clinical significance:11 of 29 patients (37.9%) could be withheld from further imaging testing.

Conclusions: Prothrombin fragment F1+2 assay may increase the proportion of patients in whom pulmonary embolism can be safely ruled out.

403 Association of the severe, frequent exacerbation phenotype with exercise capacity, sputum bacteriology and copeptin circulating levels in COPD


Background: The randomized, double-blind, double-dummy, 1-year POET-COPD™ trial compared with infrequent exacerbators in the POET-COPD™ trial.

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Results: Baseline characteristics of the 7376 patients who were randomized and treated are shown in the table.

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<th>Characteristic</th>
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<tr>
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<td>50 (IQR 40-60)</td>
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<td>FEV1% pred</td>
<td>65% (IQR 55-75%)</td>
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<td>6MWD, m</td>
<td>402 (IQR 360-545)</td>
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Conclusions: Any detectable cTnI is independently associated with increased post-exacerbation mortality, with increasing risk at higher concentrations. Excess deaths in patients with detectable cTnI occur in the first 30 days post-admission. Elucidating underlying mechanisms of cTnI rise may identify new opportunities to improve outcomes following COPD exacerbations.

404 Predictors of hospitalisation and death with acute exacerbations of COPD

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Background: Acute exacerbations of COPD (AECOPD) are common causes of attendance to hospital emergency department (ED), but there are limited data on decision making about hospitalisation.

Aims: To analyse decision making for hospitalisation and predictors of death in patients attended with AECOPD in a public hospital in Australia.

Methods: All patients with a diagnosis of AECOPD attending the ED of the Royal Hobart Hospital between November 2006 and July 2008 (21 months) were reviewed. Patients who were admitted to the hospital were compared with those who were discharged home. Survival analysis was performed using Kaplan-Meier survival analysis.

Results: 150 patients with 218 admissions (50% female, 42% current- and 58% ex-smokers, 24% with history of heart disease and 5% with previous history of myocardial infarction) were included in the study. Those discharged from ED had a lower heart rate/minute than those admitted [mean (SD) 96 (17) vs 105 (19), p<0.01] but there were no other differences. Age (HR=1.07, p<0.001), being female (HR=0.3, p=0.049) (female 80 and males1), having a past history of myocardial infarction (HR=5.36, p<0.001), hypercapnia (HR=1.04, p<0.003) and co-presence of heart disease (HR=5.7, p=0.03) were independently significant predictors of death during the period of the study.

Conclusions: Decision making for hospitalisation of patients in the ED seems largely arbitrary. Cardiac disease was the strongest predictor of death.

405 Baseline characteristics of patients with frequent exacerbations in the POET-COPD™ trial

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Background: The randomized, double-blind, double-dummy, 1-year POET-COPD™ trial showed that tiotropium (18 µg qd) was superior to salmeterol (50 µg bid) in preventing moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations.

Aims and objectives: An exploratory post-hoc subgroup analysis to compare baseline characteristics of frequent and infrequent exacerbators (patients experiencing ≥2 and ≤1 exacerbations during the trial, respectively).

Methods: Important inclusion criteria were age ≥40 years, postbronchodilator forced expiratory volume in 1 s (FEV1) ≥70% predicted and ≥1 exacerbation in previous year.

Results: Baseline characteristics of the 7376 patients who were randomized and treated are shown in the table.

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Conclusions: Compared with infrequent exacerbators, frequent exacerbators in POET-COPD™ were characterized at baseline by: more severe COPD; longer exacerbation in COPD, leading to the definition of a frequent exacerbation phenotype. We have assessed variables associated with a history of frequent, severe exacerbation according to the ERS definition in a well characterized cohort of COPD patients.

Methods: Data of 598 patients with stable COPD (GOLD II-IV) for 6 weeks, and seeking care in pulmonary tertiary hospitals in 10 European centers were analyzed. Assessment included history, systemic biomarkers (procalcitonin, proANP, copeptin, proadrenomedullin), lung function, SF-36, SGRQ, MMRC dyspnea score, and 6MWD test.

Results: Patients had a mean age of 66 years ± 12.448 were male. Mean FEV1% pred was 48.2% ± 18.5. A total of 387 patients (64.7%) reported no severe exacerbation, 170 (28.4%) reported one severe exacerbation, and 41 (6.9%) patients reported two or more severe exacerbations requiring hospitalization in previous year. ICU care was required in 45 (7.6%) of the cases. In the multivariate analysis, OR [95% CI] age 1.218 [1.043-1.422, p=0.013], positive sputum bacteriology at the stable state 8.88 [1.57-50.19, p=0.014], FEV1% pred 0.946 [0.902-0.992, p=0.021], MMRC 3.240 [1.021-10.281, p=0.040], 6MWD 1.014 [1.002-1.026, p=0.026], Borg 1.607 [1.010-5.588, p=0.045], and copeptin 0.305 [0.140-0.664, p=0.003] were independently associated with the severe, recurrent exacerbations phenotype.

Conclusions: Age, sputum bacteriology, lung function, dyspnea, exercise capacity and copeptin circulating levels are independently associated with the severe, frequent exacerbation phenotype.
## 406 BNP is a predictor of mortality following COPD exacerbations
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**Introduction:** There is a scarcity of biomarkers to predict mortality following exacerbations of chronic obstructive pulmonary disease (COPD). Pro-BNP Natriuretic Peptide (pBNP) is a measure of cardiac function, elevated pBNP levels indicate cardiac failure. We measured pBNP levels in addition to standard assessments in patients referred to our COPD admission avoidance (AA) service.

**Methods:** 33 patients (current or ex-smokers) referred for AA over a one year period had their pBNP levels checked. 6 were excluded from analysis (3 troponin positive, 1 too well, 1 refused hospital admission, 1 admitted for cardiac failure). In addition to pBNP levels, most patients had several other assessments of their lung function performed. Of the 27 patients, 4 died over the following 12 months.

**Results:** Patient mortality was associated with higher levels of pBNP (8564 ± 4959 pg/mL non-survivors vs 1162 ± 553 pg/mL survivors, p = 0.004). There were no significant differences in spirometry, MRC scores or oxygen saturations. Only 2 patients in the mortality group had a previous diagnosis of heart failure, while 7 in the non-mortality group did. Only 2 patients in the mortality group were treated for congestive cardiac failure with diuretics. None were on ACE-inhibitors or other heart failure treatment.

**Discussion:** Despite the limitations of our study (small sample size, single center, relatively homogeneous population) pBNP may prove to be a powerful predictor for mortality following an exacerbation of COPD. In addition, our findings raise the question whether any element of underlying heart failure should be treated more aggressively in patients with COPD.

## 407 Pharmacological treatment with tetrahydrobiopterin in pulmonary hypertension
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**Introduction:** Tetrahydrobiopterin (BH4), by “recouping” endothelial nitric oxide synthase (eNOS), increases NO bioavailability and decreases superoxide production. It is critical in maintaining pulmonary vascular homeostasis and may offer a treatment for pulmonary hypertension (PH).

**Methods:** BH4 administration was studied in both monocrotaline and hypoxia models of PH.

**Results:** In vivo BH4 administration (1mg bolus) caused minimal change in pulmonary artery pressure (PAP) in control rats (from 22.9 to 20 mmHg), but a significant acute reduction in the monocrotaline model (from 36 to 18 mmHg).

In a Langendorff heart preparation, BH4 increased right ventricular systolic pressure (RVSP) in the hypertrophied right ventricle (RVH) compared to control (ΔRVSP=5.7±1.3 mmHg vs 0.7±1.1 mmHg respectively, p<0.05) as well as contractility (Δdp/dtmax=640±247 vs 261±173 mmHg/sec, p<0.05).

**Discussion:** BH4 is a potential therapy which addresses the vasoconstrictive, hyperproliferative and hypertrophic nature of PH and warrants further investigation.

## 408 A role for ST2/IL-33 signalling in fibroblast proliferation utilising a novel transgenic mouse model of pulmonary hypertension
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In this study, we determined if the ST2 receptor and its ligand, interleukin-33 (IL-33) was involved in mouse PAF proliferation and if ST2-/- mice displayed a pulmonary hypertensive phenotype (RHV).

Wild type (WT) and ST2 knockout mice (ST2-/-) were used. The effect of IL-33 on proliferation of WT cells was determined by incubation in hypoxia (35mmHg), p38 MAPK, which is involved in fibroblast proliferation, was detected by Western blotting. Right ventricular hypertrophy (RVH) was assessed by measuring the right ventricular wall (RV) and left ventricle with the septum (LV-S). ST2-/- cells proliferated to a greater level compared to WT cells (p<0.01). Proliferation of ST2-/- cells could be reduced by p38 MAPK inhibition (Fig. 1).

p38 MAPK was detected in ST2-/- cells but not in WT cells. Proliferation to hypoxia in WT cells could be blocked by IL-33. The ST2-/- mice displayed right ventricular hypertrophy (Fig. 2, p<0.005).

## 409 Safety and efficacy of bosentan in combination with sildenafil in pulmonary arterial hypertension: The COMPASS-3 study
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In hypoxia, BH4 (100 mg/kg) reduced RVSP over 7 days (radioelectricity, from 63±1 to 44.5±1 mmHg). At two weeks, BH4 (100 mg/kg) partially reversed RVH compared to placebo and BH4 (10 mg/kg) (0.50±0.02, 0.58±0.03 and 0.57±0.1 respectively, p<0.05). Two weeks of hypoxia induced distal pulmonary vascular muscularization (from 15.6±2% to 79.2±7%, p<0.01). BH4 (100 mg/kg) induced partial reversal in vascular muscularization compared to placebo and BH4 (10 mg/kg) (65.2±6%, 81.4±9% and 74.3±10% respectively, p<0.01). BH4 (100 mg/kg) increased eNOS enzymatic activity in lung homogenates (but not protein levels). BH4 moderately increased cGMP (p>0.05) and significantly reduced superoxide.

Conclusions: BH4 is a potential therapy which addresses the vasoconstrictive, hyperproliferative and hypertrophic nature of PH and warrants further investigation.

## 410 70. Treatments for pulmonary hypertension in human and experimental models

### 407 Pharmacological treatment with tetrahydrobiopterin in pulmonary hypertension

Excessive proliferation of fibroblasts from ST2-/- mice involves p38 MAPK. Proliferation by hypoxia in WT cells can be blocked by IL-33. ST2-/- mice display a pulmonary hypertensive phenotype.
Effects of dasatinib and nilotinib on pulmonary vascular remodeling

Background: Tyrosine kinase inhibitors (TKIs) are used in the treatment of chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL). However, recent studies have shown that these compounds also modulate pathways involved in vascular remodeling.

Methods: To explore the effects of dasatinib and nilotinib on pulmonary vascular remodeling, we performed in vitro experiments using human pulmonary artery smooth muscle cells (HPASMCs). We examined the effects of these TKIs on PDGF-induced proliferation, cell cycle gene regulation, migration, and fibrosis.

Results: Dasatinib and nilotinib inhibited PDGF-induced proliferation and migration in HPASMCs. Treatment with dasatinib also reduced PDGF-induced fibrosis.

Conclusions: Dasatinib and nilotinib may have potential therapeutic effects in the treatment of pulmonary hypertension by inhibiting vascular remodeling.

Inhibition of microRNA-17 improves lung and heart function in experimental pulmonary hypertension

Introduction: Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disorder with high morbidity and mortality. Current treatment options are limited, and patients with PAH have a poor prognosis.

Methods: To investigate the effects of microRNA-17 (miR-17) on PAH, we used an experimental PAH model in rats. Rats were treated with a combination of PDGF and hypoxia, and the effects of miR-17 were evaluated.

Results: Inhibition of miR-17 improved lung and heart function in experimental PAH. miR-17 inhibition caused a complete reversal of pulmonary vascular remodeling and achieved efficacy similar to Imatinib (100mg/kg/day) in monocrotaline-induced PAH rats.

Conclusions: The results suggest that targeting miR-17 may be a promising strategy for the treatment of PAH.
beneficial effects in some patients in a proof-of-concept study. The phase III, multinational, multicenter, double-blind, parallel-group IMPRES study evaluated the efficacy and safety and tolerability of imatinib to confirm these preliminary findings. Patients enrolled in IMPRES had severe stable PAH on at least two PAH-specific therapies and PVR >800 dynes sec cm⁻⁵ and were randomized to imatinib or placebo. Treatment was initiated at a dose of 200 mg once daily, which was increased to 400 mg once daily after 2 weeks if well tolerated. Doses could then be reduced to 200 mg once daily if treatment was not well tolerated. The primary objective was to evaluate the efficacy of imatinib versus placebo for the change in six-minute walk distance (6MWD), a primary endpoint in the baseline treatment arms to week 24. Secondary objectives included evaluation of time to clinical worsening (all cause mortality, hospitalization for worsening PAH, worsening of World Health Organization [WHO] functional class or a 15% drop in 6MWD), safety and tolerability (including adverse events, laboratory data and vital signs), changes in pulmonary hemodynamics, changes in Borg dyspnea scores and pharmacokinetics. The study has enrolled a total of 202 patients. Findings from the IMPRES study will be available during 2011 and will be presented.

71. Recent developments in COPD

P414 LSC 2011 Abstract: The role of lipoxin A4 in the chronic obstructive pulmonary disease
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The aim: Chronic obstructive pulmonary disease (COPD) is characterized by persistent inflammatory reaction with a dominance of neutrophil involvement. It is established, that during a healing of inflammatory reaction, a switching of arachidonic acid (AA) metabolism from leukotriene (Lt) to lipoxin (LX) production occurs. Therefore we hypothesized that in COPD patients the lipoxin production could be insufficient. Here we compared the content of LXA4 and LtB4 in induced sputum supernatant (IS) in COPD patients and healthy subjects.

Materials and methods: 17 COPD patients and 7 healthy persons were studied. The age and gender ratios were similar in both groups. Sputum induction was performed according to the ERS protocol. LXA4 and LtB4 content in sputum supernatant was assessed by ELISA.

Results: COPD patients had decreased concentration of LXA4 in induced sputum compared to healthy persons (0.514 ng/ml and 3.130 ng/ml, respectively, p=0.0078). LtB4 content in induced sputum did not significantly differ between COPD group and healthy persons (3.551 ng/ml and 3.754 ng/ml, respectively). The ratio LtB4/LXA4 in COPD patients was three times higher compared to healthy persons (i.e. 9.816 ng/ml and 3.425 ng/ml, p=0.00982).

Conclusions: We concluded that the chronic obstructive lung disease is characterized by suppressed production of lipoxins. This insufficiency may be responsible for a persistence of neutrophilic inflammation in airways.

P415 LSC 2011 Abstract: Inflammation and COPD: Protective effect of the recombinant anti-protease trappin-2 A62L, on lung epithelium
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Introduction: Inflammation in chronic obstructive pulmonary diseases (COPD) results in a protease/anti-protease imbalance that leads to a massive release of neutrophil serine proteases (elastase, proteinase 3 and cathepsin G). These proteases stimulate secretion of mucus and pro-inflammatory cytokines. In order to target serine proteases, we designed a recombinant inhibitor derived from trappin-2 which is able to inhibit all three proteases at the same time. The aim of the study was to evaluate the inhibitory, anti-inflammatory and anti-secretory effects of trappin-2 A62L (T2A62L) on lung epithelium exposed to neutrophilic serine proteases.

Methods: A549 cells were exposed to proteases for 24h with or without addition of T2A62L. Protective effect of T2A62L towards the degradation of cell junctions by proteases was analyzed by immunofluorescence. Levels of mucous secretion were determined by measuring the rate of expression of mucin genes and the anti-inflammatory activity of T2A62L was investigated by measuring the rate of pro-inflammatory mediators release after LPS stimulation.

Results: Neutrophil serine proteases proteolytically degrade cellular junctions and increase mucin gene expression. T2A62L added to the culture medium inhibits the degradation of cell junctions proteins (E-cadherin, ZO-1), decreases MUC5AC and MUC5B mRNA expression induced by elastase and IL-6 and IL-8 productions.

Conclusion: Our results demonstrate that T2A62L inhibits anti-proteolytic, anti-inflammatory and anti-secretory effects. This new, anti-protease may therefore be of therapeutic value in treating inflammatory lung diseases such as COPD.

P416 Plant proteinase inhibitor from enterolobium contortisiliquum (EcTTI) attenuates elastase-induced inflammatory and remodeling alterations in mice
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Aims: To evaluate if a plant Kunitz proteinase inhibitor EcTTI contributes to in-activation of elastase-induced mechanical, inflammatory and extracellular matrix remodelling alterations.

Methods: C57Bl/6 mice received elastase (50ml/rat/mouse - IN- group) Control group received saline (Ve group). Mice were treated with EcTTI (2mg/kg) at days 1, 7, 14, 21, 28 and 35 after elastase instillation (I-E group). At day 40, mice were anesthetized, mechanically ventilated and we analyzed respiratory system resistance and elasticity, tissue elastance, damping and airway resistance. Afterwards, BAL was performed and lungs were removed. By morphometry, we quantified the mean linear intercept (Lm), collagen and elastic fibers in distal lung.

Results: There were no differences in pulmonary mechanics comparing all groups. In E-group, there was an increase in BAL-total cells, BAL-lymphocytes, BAL-neutrophils, collagen, elastic fibers and LM compared to control (p<0.05). In I-E group, EcTTI attenuated the increase in BAL-total cells (65.2±3.3×10³ cells/mL) and BAL-neutrophils (3.2±1.7×10³ cells/mL) compared to E-group (respectively: 110.7±9.7×10³ cells/mL and 80.1±4.1×10³ cells/mL, p<0.05). There was a decrease in the collagen content in I-E group (43.2±4.3%) compared to E-group (54.2±5.5, p<0.05).

Conclusions: This proteinase inhibitor (EcTTI) reduced elastase-induced pulmonary inflammatory and extracellular matrix remodeling alterations induced by elastase. Although more studies need to be performed, this inhibitor may contribute as potential therapeutic tool for COPD management.

Financial support: FAPESP, CNPq, LIM-20 HC/FMUSP.

P417 Impaired respiratory function in mice exposed to cigarette smoke
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Introduction: We have aimed to develop a mouse model of cigarette smoke (CS)-induced small airway disease and emphysema. This model will be used for studies of pathogenic responses in the development of emphysema and for preclinical evaluation of new drug candidates.

Methods: BALB/c mice were exposed to CS (nose-only), 5 days a week during 10 weeks (Gr.1: 6 cigarettes during 10 min, twice a day; Gr. 2: 12 cigarettes once a day during 20 min; Gr. 3: 12 cigarettes during 20 min, twice a day; Gr 4: control, room air). The experiment ended on day 71-73 and day 85-87 (two additional recovery weeks without CS smoke) with thoroughly investigated lung mechanics (FlexiVent), inflammatory cell counts in bronchoalveolar lavage (BAL) and lung histology.

Results: CS induced an increased respiratory resistance (p<0.05), tissue resis- tance (p<0.05), tissue elastance (p<0.05), and decreased compliance (p<0.05), in all CS groups compared to control groups. However, there were no differences in lung mechanics and total cell counts in BAL within the CS-groups. After the recovery weeks, the CS-induced effects in the lung were sustained in all groups except for Gr 2. Lung histology showed no obvious alveolar damage in peripheral airways.

Conclusion: In our mouse model there is a marked effect on lung mechanics, suggesting that CS induce small airway inflammation which is not dose dependent. Our result indicates that it is the exposure time, rather than the number of cigarettes, that determines the detrimental effects in the mouse lung. Additionally, this model can be used for combined exposure of allergens and air-borne particulate pollution in order to investigate aggravating effects of inhaled particles on emphysema and COPD.

P418 Different effects of mesenchymal stem cells on elastase-induced pulmonary emphysema and macrophages activity in rats
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The aim of the study was to assess lung tissue changes and macrophages activity (MA) after mesenchymal stem cells (MSCs) transplantation in elastase model of pulmonary emphysema in rats.
Methods: Forty 3-months old Wistar rats were randomized into 4 groups. Control group (group 1) was injected intratracheally 0.4 ml of normal saline, other animals (groups 2-4) received one intratracheal injection of 20 μl (units) porcine pancreatic elastase in 0.4 ml of saline. Next day (group 2) and 7 day (group 4) rats were intravenously injected 200000 autologous MScs in 0.5 ml of saline. Group 4 was used as emphysema control. Before killing on 21-st day rats were undergone pleural lavage with analysis of hemi-luminescent macrophages activity in the obtained fluid.

Results: The lungs of groups 2-4 had various degrees of centriacinar emphysema. There were no significant differences between the sizes of dilated respiratory bronchioles in groups 2 & 4. Only in the 2nd group we observed the lymphoid infiltration around arterioles. The width of respiratory bronchioles in group 3 was on 41% less than in the 4-th. The Index of hemi-luminescent MAA has made 28.8±1.1 U (1 group), 35.8±1.6 U (2 group), 31.9±4.1 U (3 group), 57.3±3.1 U (4 group).

Conclusions: MScs have various effects on damaged lung tissue at different periods of transplantation. MScs can enhance the local vascular inflammatory response in the early period of lung injury. More later injection of MScs can repair the structure of acini in acute model of emphysema in rats.

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IL-10 resolves the neutrophilic inflammation in mice exposed to cigarette smoke

Manabu Higaki1, Hiroo Wada1, Tetsuo Yasutake1, Shinichiro Mikura 1

Introduction: IL-10 plays a suppressive role in the inflammation. In order to elucidate the role of IL-10 in the inflammation caused by cigarette smoke, mice exposed to cigarette smoke were investigated.

Materials & methods: Mice (C57BL/6) were exposed either to cigarette smoke or to environmental air for 5, 8 or 12 days. To characterize the inflammation, cellularity in bronchoalveolar lavage (BAL) fluid was investigated. The levels of inflammation-associated cytokines, such as IL-10, KC, MIP-2, TNF-α and GM-CSF were further determined by measuring both mRNA levels in the lungs and the protein levels in BAL fluid. Then, a group of mice was intranasally treated either with recombinant murine IL-10 or with vehicle and exposed to cigarette smoke, before the same analysis was performed.

Results: Cigarette smoke exposure provoked pulmonary inflammation in mice as neutrophil and macrophage counts in BAL fluid were increased (p<0.01). In parallel, the levels of various proinflammatory cytokines including KC and MIP-2 significantly increased (p<0.01), as did the IL-10 expression. The SVL in the neutrophil counts in BAL fluid caused by smoke exposure was significantly attenuated by the intranasal administration of IL-10 (p<0.05), while that in macrophage counts was not altered.

Conclusion: Our results suggested that IL-10 potentiates the suppression of the neutrophil-associated inflammatory reactions caused by cigarette smoke exposure.

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Activation of the inflammasome pathway during exacerbations of COPD

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Introduction: Exacerbations of COPD (ECOPD) are characterized by a burst of inflammation. The inflammasome is an intracellular sensing mechanism that leads to activation of caspase-1 and processing of pro-IL-1β and pro-IL-18 into their mature forms.

Aim: To investigate if the inflammasome pathway is activated in ECOPD patients.

Methods: We studied 10 COPD patients hospitalized because of ECOPD, 7 of whom were revaluated 3 months after discharge (sECOPD), 13 patients with clinically stable COPD (SCOPD), 8 smokers with normal lung function (S) and 11 non smokers (NS). We determined: (1) in serum: caspase-1, IL-1β, IL-18, IL-1Ra, IL-6, IL-8 and TNF-α; (2) in circulating monocytes and lymphocytes: intracellular activity of caspase-1 (basally and after stimulation with inflammasome ligands: ATP, Nigercine and Cigarette Smoke Medium); and (3) in whole blood: caspase-1 and NLRP3 mRNA.

Results: Table 1 shows main results (mean ± SD).

Conclusions: The inflammasome pathway participates in the inflammatory burst that characterizes ECOPD.

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Effect of budesonide on fibroblast-mediated collagen gel contraction and degradation

Qinhong Fang1, Nancy Schulte2, Xิงgai Wang1, Anna Miller-Larsson3, Pavitra Wiestlander1, Xingyi Wang1, Myron Toews2, Stephen Rennard1

Background: IL-18, IL-1Ra, IL-10 have anti-inflammatory effects, but its effect on fibroblast-mediated tissue repair and remodeling has not been fully studied.

Materials: Using human fetal lung fibroblasts (HFL-1 cells) in a three-dimensional collagen gel culture system, the current study investigated the effect of budesonide (1-1000 nM) on collagen gel contraction and degradation in the presence or absence of inflammatory cytokines (IL-1β and TNF-α: 5 ng/ml each) and, in order to activate latent proteases, the serum trypsin (0.25 μg/ml).

Results: Inflammatory cytokines significantly inhibited collagen gel contraction mediated by lung fibroblasts. Budesonide counteracted the effect of cytokines in a concentration-dependent manner (p<0.01). Budesonide (100 nM) almost completely inhibited the release and mRNA expression of metalloproteinases (MMP)-1, -3 and -9 induced by the cytokines (p<0.05). Exposure to the cytokines provoked increased collagen degradation and activation of the MMPs. Budesonide blocked both the enhanced collagen degradation (p<0.01) and suppressed the trypsin-mediated activation of cytokine-induced MMP-9 and MMP-3. Similar effects were observed with dexamethasone (1 μM), suggesting a class effect.

Conclusions: These findings suggest that budesonide directly modulates contraction of collagen and can decrease collagen degradation under inflammatory conditions through suppressing release and activation of MMPs. By modulating the release and activity of MMPs, inhaled budesonide may be able to modify airway tissue repair and remodeling.

P422

Sputum lipid profile and iron content in serum and pulmonary tissue in experimental pulmonary emphysema

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Introduction: To investigate if the inflammasome pathway is activated in ECOPD patients.

Materials: Using human fetal lung fibroblasts (HFL-1 cells) in a three-dimensional collagen gel culture system, the current study investigated the effect of budesonide (1-1000 nM) on collagen gel contraction and degradation in the presence or absence of inflammatory cytokines (IL-1β and TNF-α: 5 ng/ml each) and, in order to activate latent proteases, the serum trypsin (0.25 μg/ml).

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Conclusions: These findings suggest that budesonide directly modulates contraction of collagen and can decrease collagen degradation under inflammatory conditions through suppressing release and activation of MMPs. By modulating the release and activity of MMPs, inhaled budesonide may be able to modify airway tissue repair and remodeling.

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P423  
Inhibition of β-adrenoceptors alleviated mucus secretion and emphysema in cigarette smoke exposed rat model  
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Background: The sympathetic nervous (SN) is probably over activated in COPD. Some retrospective studies found that treatment with β-blockers may reduce the risk of exacerbations and improve survival in COPD patients. However, our preliminary data showed that no significant change of lung function in COPD patients after treatment with β-blocker. The aim of the study is to elucidate whether inhibition of the SN over activation may improve lung pathological change in smoke exposed rat model.  

Methods: The rats were randomly divided into 3 groups: control group (C, n=9), smoke-exposed group (S, n=8) and smoke-exposed plus propanolol group (S/P, n=8). S and S/P rats were exposed to cigarette smoke for 3 months, and S/P rats were further treated with propanolol for 1 month. Lung tissue pathologic score and mucus (MLI) were determined.  

Results: The scores of mucus secretion, goblet-cell metaplasia, smooth muscle cells (SMC) proliferation, and MLI were significantly different in the 3 groups (see table 1), however, no significant difference was found in other aspects of pathological changes.  

Table 1. Lung tissue pathologic scores in the 3 groups (mean ± SD)  
<table>
<thead>
<tr>
<th>Group</th>
<th>Mucus secretion</th>
<th>Goblet-cell metaplasia</th>
<th>SMC proliferation</th>
<th>MLI (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>7.06±5.53</td>
<td>0.17±0.94</td>
<td>0.23±0.18</td>
<td>30.78±2.29</td>
</tr>
<tr>
<td>S</td>
<td>17.64±4.62*</td>
<td>1.66±0.79a</td>
<td>0.79±0.55</td>
<td>47.46±4.96</td>
</tr>
<tr>
<td>S/P</td>
<td>9.78±5.98*</td>
<td>0.96±0.55</td>
<td>0.83±0.71</td>
<td>39.47±2.56</td>
</tr>
</tbody>
</table>

P value 0.005 for S/P vs S, *P<0.01 for S/P vs C, &P<0.01 for S vs C, § P<0.05 for C vs S/P, †P<0.01 for S vs C, ¶ P<0.05 for C vs S/P, ‡P<0.01 for S vs C.  

Conclusion: In cigarette smoke exposed rat model, inhibition of β-adrenoceptors alleviated mucus secretion and emphysema.  

P424  
AMPK signalling regulates Nrf2 localization and activity via sirtuins in a monocytic cell line  
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Nrf2 participate in the defence against oxidative stress by inducing anti-oxidant genes such as HO-1 and NQO1, which system is downregulated in COPD. AMPK and sirtuins are ageing related signals reported to control the expression of genes. Sirt1 is also down-regulated in COPD lung.  

Aims: To evaluate the effect of sirtuin inhibition and AMPK activation/inhibition on the nuclear localization and activity of Nrf2, and the expression of HO1 and NQO1.  

Methods: THP-1 monocytic cells were treated with a sirtuin inhibitor (sirtinol), hydrogen peroxide (H2O2) as oxidative stress reagent and AICAR and dorsomorphin as AMPK activator and inhibitor respectively. Nrf2 protein levels were measured by western blot and the samples were normalized against Lamin A/C. The mRNA levels of HO1 and NQO1 were measured by RT-PCR and normalized to 18S.  

Results: H2O2 increased Nrf2 in the nucleus by 2-fold and pretreatment with sirtinol did not affect this induction. In contrast, although Nrf2 binding activity also increased by 50% with H2O2, preincubation with sirtinol abrogated this activation. Dorsomorphin treatment provoked a decrease in the nuclear levels of Nrf2 by 50% with H2O2, preincubation with sirtindol abrogated this activation. These results may explain the increased tobacco smoke susceptibility in early stages to develop lung emphysema with the C57 strain, as compared to the less susceptible strain, 129S2.  

Conclusion: These results explain the increased tobacco smoke susceptibility in early stages to develop lung emphysema with the C57 strain, as compared to the less susceptible strain, 129S2.  

P425  
Molecular markers involved in susceptibility to lung injury after acute exposure to tobacco smoke in different mouse strains. Fluorescent molecular in vivo imaging application  
Sandra Pérez-Rial, Laura del Puerto-Nevado, Álvaro Girón-Martínez, Raúl Terrén-Expósito, Nicolás González-Mangado, Germán Pérez-Barba. Pulmonology, IIS-Fundación Jiménez Díaz, Madrid, Spain  

Mouse strains C57 and 129S2 show different susceptibility to developing COPD when they are exposed chronically to tobacco smoke. The aim of this study is to determine molecular differences, between these two strains in the early stages of the disease within 24, 48 and 72h of being acutely exposed to tobacco. We quantified the levels of MMP-12 and analyze MMPs activity in lungs of mice by fluorescence molecular imaging techniques using MMPs activable fluorescent probe. We also measure NF-κB and TNF-α levels. The results in C57 strain showed a significant increase in MMPs activity measured at 24 and 48h of cigarettes exposure while 129S2 did not observed changes.  

In addition, MMP-12 levels increased significantly in C57, but not in 129S2 strain. Respect to the studied of NF-κB, significantly increased at 24 and 48h, in correlation with an increase in the levels of TNF-α, only in C57.  

Although COPD is one of the leading causes of morbidity and mortality in the world, until now there is no effective treatment to improve lung function in COPD patients. Animal models have been employed to better understand the pathophysiology of this disease and to test new therapies.  

Objectives: To evaluate the effects of a protease inhibidor in emphysema.  

P426  
Effects of a protease inhibitor from the tick rhizophilus boophilus microplus in an experimental model of emphysema  
Clarice Oliveira1, Luana Neves1, Juliana Lourenço1, Fruncine Almeida1, Carla Prado2, Iolanda Tibério1, Aparecida Tanaka2, Sergio Sasaki3, Milton Martins1, Fernanda Lopes1, 1Department of Medicine, Universidade de São Paulo, Sao Paulo, Brazil; 2Department of Biological Science, Universidade Federal de São Paulo, Sao Paulo, Brazil; 3Department of Biochemistry, Universidade Federal de São Paulo, Sao Paulo, Brazil. 4Human and Natural Science, Universidade Federal do ABC, Sao Paulo, Brazil  

These results may explain the increased tobacco smoke susceptibility in early stages to develop lung emphysema with the C57 strain, as compared to the less susceptible strain, 129S2.
Methods: 40 C57BL/6 mice received either a nasal instillation of 50 μl (0.667 UI) of porcine pancreatic elastase (PPE) or saline (S) and 1 h after, animals received a second nasal instillation of 50 μl of either a prototype inhibitor (r-BmTIA, 35.54pmol) or vehicle (VE). After 21 days, animals were anesthetized and airway resistance (RAW), tissue damping (G(t)) and tissue elastance (Hz(t)) were measured using Flexivent small animal ventilator. After sacrifice, lungs were removed and formalin-fixed for posterior analysis of mean linear intercept (Lm).

Results: We observed a decrease in Hz(t) values only in PPE-VE group [Fig. 1A]. Lm values were increased in PPE-VE and PPE-BmTIA groups, whereas the PPE-BmTIA showed a decrease in Lm values when compared to PPE-VE group [Fig. 1B]. There was no difference in G(t) and Raw values [Fig. 1C and Fig. 1D, respectively].

Conclusions: We showed that a single dose of this prototype inhibitor attenuated parenchyma destruction in an experimental model of emphysema. Supported by FAPESP, LIMHC-FMUSP CNPq, Brazil.

P427
HDAC2-independent anti-inflammatory effects of budesonide in human lung fibroblasts
Xingqi Wang1, Amy Nelson1, Anna Miller-Larsson2, Elisabet Wieslander2, Xiangde Liu1, Stephen Rennard 1.

Background: Reduced response of COPD patients to the anti-inflammatory therapy with glucocorticoids may be due to reduced expression of histone deacetylases (HDAC) in alveolar macrophages and bronchial epithelial cells as suggested by recent studies. Lung fibroblasts release inflammatory mediators and are key cells in tissue remodeling following airway inflammation. However, HDAC expression and its role in mediating glucocorticoid effect on fibroblast functions have not been studied.

Methods and results: Human fetal lung fibroblasts (HFL-1) were exposed to IL-β + TNF-α (5ng/ml each), while stimulated of IL-β, IL-8 and metalloproteinase (MMP-1 and MMP-3). These responses were inhibited by the glucocorticoid budesonide (0.1-100nM) in a concentration-dependent manner. An HDAC inhibitor (trichostatin A) did not reverse the effects of budesonide on release of cytokines and MMPs. While it blocked the inhibitory effects of budesonide on human bronchial epithelial cells and monocytes. Furthermore, siRNA targeting HDAC2 did not interfere with the inhibitory effects of budesonide on HFL-1 MMP release. Exposure to cigarette smoke extract (5%) did not affect HDAC2 expression in HFL-1 cells and did not interfere with the budesonide effects. Finally, there was no statistically significant difference between COPD and control subjects in HDAC2 expression and the effects of budesonide on cytokine or MMP release from lung fibroblasts.

Conclusions: HDAC2 is not required for budesonide to inhibit MMP and cytokine release by lung fibroblasts. These results also suggest that budesonide has a potential to counteract fibroblast-mediated tissue remodeling following airway inflammation in COPD.

P428
The nuclear liver X receptor and its role in smoke exposed rat lungs
Adelheid Kratzer, Jonas Salys, Martin Zamora, Laina Taraseviciene-Stewart

Background: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality worldwide and currently there are no efficient treatments. Liver X receptor (LXR) plays a role in lipid metabolism and inflammation. Treatment with LXR agonists has been shown to improve lung function in COPD patients.

Methods: Sprague Dawley rats were exposed to smoke for two months. The lung tissue and bronchoalveolar lavage (BAL) cells were examined for LXR target gene expression and emphysema development was measured by MLI. Rat AM and EC treated with LXR agonist were examined for LXR target gene and protein expression and migratory capacity. LXR2 localization before and after exposure was determined by immunofluorescence.

Results: Whereas expression of ATP binding cassette transporter A1, a known LXR target gene, was not changed in the lung, but significantly downregulated in the BAL cells from smoke-exposed rat lungs and in smoke-exposed treated AM. Immunofluorescence showed reduced nuclear localization of the anti-inflammatory LXRα isoform in AM and pulmonary EC. Activation of LXR attenuated LPS-induced genes such as COX2, CCL5 and IL1β, but upregulated IL18 binding protein (IL-18BP), an endogenous IL-18 inhibitor. It increased the migratory capacities of rat alveolar macrophages towards CCL5.

Conclusions: Activation of LXR attenuated the pro-inflammatory cytokine production by AM suggesting that LXR agonist treatment might be beneficial to prevent and treat COP-emphysema.

P429
Insulin-dependent PI3-Kinase/Akt and ERK signaling pathways inhibit TLK3-mediated HBECC apoptosis
Takamori Numata1, Jun Araya1, Satoko Futaji 1, Hiromichi Harase 1, Naoki Takasaka1, Yoko Yumino1 , Makoto Kawashina 1, Jun Hirano2, Makoto Odaka2, Toshiaki Morikawa2, Katsutoshi Nakayama 1, Kazuyoshi Kuwano1.

TLK3, a novel tumor suppressor, inhibits proliferation, invasion and is necessary for HBECC apoptosis. Recent studies suggest that, in addition to PI3K/Akt and ERK pathways, ways via NF-κB and mitochondrial pathways are involved in this process. However, the roles of PI3K/Akt and ERK pathways in TLK3-mediated apoptosis need to be clarified. Therefore, the aim of this study is to investigate the role of PI3K/Akt and ERK pathways in TLK3-mediated HBECC apoptosis.

Methods: A549 and 16HBE cells were cultured with IL-1β and TNF-α. The effect of PI3K/Akt and ERK pathways was studied using specific inhibitors. The apoptosis was assessed using Annexin V staining. Results: PI3K, Akt and ERK pathways were involved in TLK3-mediated apoptosis. The combination of Akt and ERK inhibitors showed a synergistic effect. Conclusion: PI3K/Akt and ERK pathways play a critical role in TLK3-mediated HBECC apoptosis.

P430
Overexpression of RAGE in lungs of patients with COPD: A contributor to oxidative stress in COPD
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Background: Receptor for advanced glycation end products (RAGE) has been recently suggested to be implicated in COPD, although the mechanisms remain unclear. The aim of this study is to investigate the expression of RAGE in lungs tissues from COPD patients and its potential role in oxidative stress in COPD.

Methods: Peripheral lung tissue specimens were obtained from 40 patients who underwent lung resection for non-small cell lung cancer, including 8 non-smoker controls, 7 non-COPD smokers and 25 smoker COPD patients. Immunohistochemistry and ELISA were used to assess RAGE expression in lung tissues, and oxidative stress was also measured by ROS and GSH. Furthermore, human pulmonary epithelial cell (AS49) and bronchial epithelial cell (16HBE) were cultured with cigarette smoke extract (CSE). Neutralizing antibody against RAGE was used to detect the role of RAGE in oxidative stress in COPD.

Results: RAGE expression level in smoker COPD patients was significantly higher than non-smoker controls and non-COPD smokers, which was dominantly expressed in the bronchiolar and alveolar epithelia. Importantly, RAGE in smoker COPD patients was positively correlated with oxidative stress, evidenced by levels of ROS and GSH. In the in-vitro study, CSE enhanced oxidative stress level in AS49 and 16HBE cells, as well as activation of NF-κB, a key redox transcription factor, which were all reversed by pretreatment of anti-RAGE antibody.

Conclusion: Overexpression of RAGE may contribute to COPD pathogenesis, at least partly through enhancement of oxidative stress level.

P431
MMP-mediated regulation of ENaC channel in pleural mesothelioma
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1Physiology Department, University of Thessaly, Larissa, Greece; 2Respiratory Department, University Hospital of Thessaly, Larissa, Greece

Introduction-aim: The epithelial sodium channel (ENaC), which participates in sodium reabsorption across the apical membrane of mesothelial cells, has been recently identified in pleura with molecular techniques. MMP2 and MMP9 are two matrix metalloproteinases (MMPs) that have been found elevated in exudative pleural effusions. The aim of this study was to investigate if MMP2 and MMP9 influence functionally ENaC activity.

Methods: Intact sheets of parietal pleural tissue were obtained and the short-circuit current (Isc) was recorded in Ussing chambers. MMP2 (0.1 ng/ml or 20 ng/ml) or MMP9 (0.1 mg/ml or 20 mg/ml) were added on the apical solution of the pleura. A 40 min incubation, amiloride (10-4 M) was added to the apical compartment of all experiments in order to calculate the ENaC-mediated current. This current was defined as the difference between the Isc value just before amiloride addition and the Isc value 5 min after amiloride addition. The amiloride-sensitive Isc was compared between control tissues (having received only PBS) and tissues treated with MMP2 or MMP9.
Results: A statistically significant decrease in amirolide-sensitive Isc occurred when 20 ng/ml MMP2 were added to the pleura (p<0.05). When the pleura was incubated with 0.1 mg/ml MMP2 or MMP9, an increase in amirolide-sensitive Isc occurred but this was not statistically significant.

Conclusions: According to the above results, MMP2 regulates ENaC activity by decreasing the sodium current which is produced by ENaC. A same effect for MMP9 was not confirmed. Previous studies have shown a serine-peptidase mediated regulation of ENaC activity. This is the first study that suggests a matrix-metalloproteinase-mediated downregulation of ENaC activity.

72. Genetics of airway diseases and treatment

P432

LSC 2011 Abstract: Association of IL-9 and IL-4R genes and their phenotypes among Sudanese with asthma

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Background: Asthma is a “complex” heritable disorder, candidate genes that may be involved in the pathogenesis of asthma including: interleukin 4 (IL-4), IL-5, IL-9, and IL-13 (Postma et al. 1995). Asthma prevalence in Sudan was found to be 12.5% in children aged 13-14 year in the Capital Khartoum (Mohamed et al. 1999).

Objectives: To detect polymorphisms of IL-9 in chromosome 5 and IL-4R in chromosome16 contributing to asthma and to estimate the environmental components: total immunoglobulin E levels, skin prick test, and eosinophil count in Sudanese population.

Methods: Seventy, nuclear and extended families were sampled in the initial phase of the study. Ventilatory function, skin, prick test blood sample for DNA analysis, immunoglobulin E, eosinophil count were carried out in the whole sample. Genotypes for IL-9, IL-4R and IL-13, polymorphisms using PCR were also carried out for a subset of the sample.

Results: Phenotypic analyses of the pedigrees suggest a likely genetic cause for asthma, as shown in one extended family. Level of total immunoglobulin E was found to be 71% in asthmatic, and 24% in non asthmatic. Eosinophil count was found to be 58% in asthmatic, while found to be 17.4% in non asthmatic. Hypersensitivity symptoms to six allergens showed positive skin test. (p = 0.00).

Genotyping for IL-9, IL-4R suggest the presence of association for both IL-9 and IL-4R (P=0.008/0.007).

Conclusions: Asthma runs in families showing strong linkage to genes. There seems to be sufficient phenotypic and genotypic indicators to suggest a genetic predisposition component to asthma among Sudanese, and warrant some further investigations.

P433

Polymorphisms in toll-like receptor 4 are associated with severity but not susceptibility for asthma in a Chinese Han population

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Background: Toll-like receptor 4 (TLR4) links human innate and adaptive immunity via bacterial endotoxin recognition, and has a considerable role in the pathogenesis of asthma. The effects of the genetic variants in TLR4 on asthma are still largely unknown.

Aims and objectives: This study aimed to evaluate the effects of polymorphisms in TLR4 on asthma risk and asthma-related phenotypes in a Chinese Han population.

Methods: We consecutively recruited 318 unrelated adult asthmatic patients and 352 healthy volunteers. Four tagging single nucleotide polymorphisms (SNPs) in TLR4 gene were detected using GenomeLab SNPStream or TaqMans Genotyping. We conducted case-control and case-only association studies between the selected tagging SNPs in TLR4 and asthma or asthma-related phenotypes.

Results: We found no evidence to support a significant association between TLR4 SNPs and asthma susceptibility. However, our results revealed that the TT homozygote of rs1927914 was associated with lower FEV1,% in asthmatic patients. An evidently positive association was found between the TT genotype of rs1927914, or the GG genotype of rs10983755 and rs1927907, and asthma severity (P=0.024, 0.009, 0.013, respectively), which indicated that the C allele of rs1927914, and the A allele of rs10983755 and rs1927907 had a protective effect on asthma severity. Conclusion: TLR4 polymorphisms do not contribute to asthma susceptibility, but may influence the severity of asthma.

P434

Vitamin D binding protein variants associate asthma susceptibility in a Chinese Han population

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Background: Asthma is a genetically heterogeneous disease. Polymorphisms of genes encoding components of the vitamin D pathway have been reported to associate with the risk of asthma. Previously, we demonstrated that the vitamin D status in serum was associated with lung function in Chinese asthma patients. In this study, we tested whether polymorphisms of vitamin D receptors (VDR), vitamin D 25-hydroxylase (CYP2R1) and vitamin D binding protein (GC) were associated with asthma in a Han Chinese Population.

Methods: We sequenced 8 exons of VDR and all 5 exons of CYP2R1 and identified only two mutations on the coding regions in a Han Chinese case-control cohort of asthma. These two polymorphism markers were rs2228570 on exon 4 of VDR and rs12794714 on exon 1 of CYP2R1. We then genotyped the two markers in the cohort that consisted of 467 asthma patients and 288 unrelated healthy. We also genotyped two common polymorphism marker rs4588 and rs7041 in vitamin D binding protein (group-specific component, GC) gene by a PCR-restriction fragment length polymorphism (RFLP) method. We analyzed the association between these polymorphisms and asthma susceptibility and asthma relevant traits.

Results: Polymorphism markers in VDR and CYP2R1 were not associated with asthma in the Han Chinese cohort. The variants of vitamin D binding proteins were associated with asthma susceptibility. Compared with GC1, GC2 was strongly associated with the risk of asthma (OR=3.95, 95% CI: 1.01-1.78 p=0.006).

Conclusions: The results provide supporting evidence for association between GC variants and asthma susceptibility in the Chinese Han population.

P435

Is there a relation between asthma associated polymorphisms and recurrent wheezing in preschool children? The ADEM study

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Background: About 20-40% of preschool children experience wheezing. One in three wheezers will have persistent symptoms after the age of six and develop asthma. It is unknown which gene variants contribute to wheezing.

Aim: To explore the relation between asthma associated single nucleotide polymorphisms (SNPs) and preschool recurrent wheezers.

Methods: We selected 202 recurrent wheezers (ISAC questionnaire ≥2 wheezing episodes) and 50 controls aged 2-4 years. Saliva and buccal swabs were used for DNA extraction. Chi square tests were performed on 23 SNPs in 15 genes. Results were expressed in unadjusted odds ratio (OR) with 95% confidence interval. Multiple testing was corrected by the Benjamini and Hochberg False Discovery Rate.

Results: In total 134 boys and 116 girls participated with an average age of 3.3 years. All SNPs had a high call rate (94.3-99.2%). The frequencies of a genetic variant in ADAM33 (rs1511898) differed statistically significantly between cases and controls leading to OR=2.4 (1.2-4.9) for CT genotype and OR=1.0 (0.4-2.5) for TT genotype compared to CC genotype (p=0.03). The frequencies of a genetic variant in ORMDL3 (rs7216389) differed statistically significant between cases and controls leading to OR=3.7 (1.7-8.2) for CT genotype and OR=2.7 (1.2-6.3) for TT genotype compared to CC genotype (p<0.01). Neither remained statistically significant after multiple testing correction (rs511898 p=0.36, rs7216389 p=0.07).

Conclusions: We observed some evidence for the association of the ORMDL3 SNP rs7216389 and recurrent wheeze. The T-allele was more frequent in recurrent wheezers, which is consistent with previous studies in asthma.

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Association of ADAM33 gene polymorphisms with asthma in Volga-Ural region of Russia

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ADAM33 is the first reported asthma-susceptible gene identified by positional cloning. ADAM33 is located on chromosome 20q13 and codes for a protein
P437
Use of partition tree to identify genetic marker combination predicting bronchodilator response by inhaled short-acting beta 2 agonist
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Objective: To identify genetic marker to predict bronchodilator response by inhaled short-acting beta 2 agonist after methacholine-induced bronchoconstriction.

Methods: A total of 480 patients were enrolled, who showed ≥20% decrease of FEV1 in methacholine bronchial provocation test and subsequently inhaled 2 puff of salbutamol (200 mcg), then FEV1 was re-measured 10 minutes later. Twenty SNPs in 10 genes related with airway inflammation, structural changes, or smooth muscle function was scored by high throughput technique. They were TNF-α (-308A>G), IL13 (-1143C>A), IL5RA (-3232C>T), IL4RA (-128C>A), VEGFR2 (889G>A, 1416A>T), TGFBR3 (44T>C), 2753G>F, 464R (28A>G, 1162G>A, 538A>G, CS2P (536C>T), IL3 (80F>C) and ADRβ2 (79C>G). The partition tree was used to investigate SNP combinations. The first partition was done by SNP discrimination of responders from non-responders based on dominant model of minor frequency allele. Then subsequent partition was performed by the other SNPs until statistical significance disappeared.

Results: The SNP-201G>A in VEGFR1, was the most significant and used in the first partition (25.7±19.8% vs. 20.0±13.8% increase, p<0.001). The best responders with AA or AG of -201G>A and CC of -1111C>T were discovered after second partition (30.3±16.7% increase). The poorest responders with GG of -201G>A, GG of 2753G>F and GG of 1162G>A were discovered after third partition (17.2±15.4% increase).

Conclusion: The combination of genetic markers related to the airway inflammation or structural changes can be used in predicting bronchodilator response by short-acting β2 agonist.

P438
Association between beta2 adrenergic receptor (ADRβ2) haplotype pair and severe asthma in an Australian caucasian population
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Background: Studies in mild asthmatics showed adverse outcomes with chronic use of short or long acting beta agonists in individuals with β2 adrenergic receptor (ADRB2) polymorphisms including ADRB2+46G>C. The extent to which ADRB2 polymorphisms contribute to severe asthma is unknown, hence the association of ADRB2 polymorphisms with asthma severity was investigated.

Methods: Multidrug resistance gene (MDR1) encodes P-glycoprotein 170 (Pgp170), which realizes efflux of glucocorticosteroids (GCS) from the cell. C3435T of gene MDR1 in genotype if compared with geterozygous ones: 2.86 mg/day vs 1.86 mg/day (p=0.041). Alpha-1 adrenergic receptor (ADRA1) polymorphism on the airway response to cold air in asthmatics
Dena E. Naumov1, Julius M. Perelman1, Vladimir N. Maksimov2, Viktor P. Kolesov3, Xiondong Zhou4, Qi Li4, Laboratory of Functional Research of Respiratory System, Far Eastern Scientific Center of Physiology and Pathology of Respiratory System SB RAMS, Blagoveschensk, Russian Federation; 2Molecular Genetics Research Laboratory, Scientific Research Institute of Therapy SB RAMS, Novosibirsk, Russian Federation; 3Division of Respiratory Medicine, Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

Background: Previously we’ve found out that the decline in β2-adrenoceptors (β2-AR) function affects airway response to cold air.

Objective: The aim of our study was to reveal the contribution of Arg16Gly SNP (rs1042713) in the development of cold air hyporesponsiveness (CAH) in asthmatics.

Methods: The study included examination of 60 mild to moderate asthmatics of Caucasian race, mostly non-smokers (mean age 36±1.39). All the patients underwent spirometry before and after the challenge with 3-minute isocapnic (5% CO2) hypercapnia (ICAH). More than 10% drop in FEV1 was interpreted as a positive result. Intracutaneous cyclic adenosine monophosphate (cAMP) concentration in lymphocytes was measured before and 30 min after ICAH under in vitro stimulation with 10M M epinephrine. PCR-RFLP analysis was used for genotyping.

Results: Arg16Gly genotype dominated in the group with CAH (χ2=7.47; p=0.005). Mean FEV1, drop differed between homozygous patients (16.0±2.7% at Arg vs 8.6±1.1% at Gly, p=0.004). cAMP concentration didn’t depend on genotype before the challenge, but 30 min after there was a significant fall in cells ability to produce cAMP in subjects with Arg16Gly genotype (p=0.03). Moreover, Arg16 homozygotes had lower cAMP levels as compared to Gly16 (48.32±6.16) and 78.59 (81.3) pmol/10^6 cells, respectively, p=0.0048. In patients with allele C bronchial obstruction was less severe. However, if compared with TT genotype, post-broncholytic increase of velocity characteristics and SGRG were not good responders from poor to dominant model of minor frequency allele. Then subsequent partition was performed by the other SNPs until statistical significance disappeared.

Conclusion: Patients with allele C require higher α2GCS doses, probably, due to enhanced activity of Pglycoprotein and accelerated GCS efflux. In patients with TT genotype significant obstruction may be due to inadequate O2GCS dose, while reversibility of distal obstruction may be due to intact function of bronchial smooth muscles and their sensitivity to GCS.

P440
Effect of ADRB2 polymorphism on the airway response to cold air in asthmatics
Denis E. Naumov1, Julius M. Perelman1, Vladimir N. Maksimov2, Viktor P. Kolesov3, Xiondong Zhou4, Qi Li4, Laboratory of Functional Research of Respiratory System, Far Eastern Scientific Center of Physiology and Pathology of Respiratory System SB RAMS, Blagoveschensk, Russian Federation; 2Molecular Genetics Research Laboratory, Scientific Research Institute of Therapy SB RAMS, Novosibirsk, Russian Federation; 3Division of Respiratory Medicine, Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

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A common characteristic of COPD and bronchial asthma is the chronic inflammation in the airways. In the current case-control study we investigated -511C>T promoter polymorphism and +3953C>T silent polymorphism of IL1B and their haplotypes as candidate risk factors of COPD and Bronchial asthma. We genotyped 163 patients with COPD, 47 with Bronchial asthma and 174 control individuals using Taqman genotyping assay for IL1B -511C>T and PCR-RFLP-based method for +3953C>T.

We did no observed significant differences in genotype frequencies of studied SNPs between controls and patients both with COPD and asthma, however the minor T allele of IL1B -511C>T was less frequently found in controls (0.305) than the patients with COPD (0.377, p=0.046) and especially with asthma (0.415, p=0.026). The carriers of IL1B -511C>T TT allele (TT and TC genotypes) had 1.56-fold higher risk for development of COPD (p=0.045) and 2.25-fold higher risk of Bronchial asthma (p=0.019). The performed estimations of IL1B haplotypes showed that T_C haplotype (alleles found to determine enhanced expression of IL-1β), appeared to be associated with higher risk of COPD (OR=1.25, p=0.231) and asthma (OR=1.78, p=0.035) compared to the most common C_C haplotype and with 1.70-fold higher risk of COPD (p=0.018) and 1.37-fold higher risk of asthma (p=0.313) compared to the C_T haplotype, associated with lower IL-1β expression.

We suggest that the -511C>T promoter SNP and +3953C>T silent polymorphism of IL1B may influence the genetic predisposition of COPD and Bronchial asthma: the carriers of alleles and haplotypes supposed to define higher IL-1β levels are more susceptible for these diseases.

Conclusions: These data suggest a definite proof for contribution of primary β2-AR dysfunction into the development of CAHR in our population sample. CAHR was strongly associated with Arg16Arg genotype. Blunted cAMP response in Arg/Arg subjects indicates inherited predisposition of their β2-AR to acute desensitization during the ICAH.
Results: There were 6 SNPs significantly associated with risk of grade 3 or 4 hematologic toxicity in platinum-based treatment. The variant homozygotes of rs12934241 exhibited the most significant influence on the occurrence of severe neutropenia (P=9.3×10^-3). In stratification analysis by chemotherapy regimens, we found the greatest correlations in patients receiving cisplatin-gemcitabine: 7 polymorphisms were found to be associated with severe neutropaenia, especially rs12934241 (2.5% for C/C vs 66.7% for TT; P=9.4×10^-7). Consistent results were found in MMP-2 haplotype analyses. In patients receiving cisplatin-navelbine, we also observed 6 SNPs significantly associated with grade 3 or 4 hematologic toxicity. However, in cisplatin-carboplatin-paclitaxel treatment groups, no correlation with such toxicity was found.

Conclusions: Our study, for the first time, provides evidence for the predictive role of MMP-2 polymorphisms on severe chemotherapy-related hematologic toxicity variability among platinum-treated advanced NSCLC Chinese patients.

P446
EGFR, HER2 and KRAS mutational status according to adenocarcinoma patterns/sub-types
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Lung adenocarcinomas represents about 42% and 28% of NSCLC diagnosed in women and men. Several subtypes are recognized by WHO. EGFR, HER2 and KRAS mutations have been described. Authors intends to identify differences between adenocarcinomas subtypes/patterns concerning EGFR, HER2 and KRAS mutations, gene copy number and protein expression.

45 lung adenocarcinomas were evaluated for EGFR, HER2 and KRAS mutational status by PCR, fragment analysis and direct sequencing. EGFR and HER2 gene copy number by fluorescence in situ hybridization (FISH). EGFR and c-erbB-2 protein expression was determined by immunohistochemistry (IHC).

8 cases showed EGFR exon 21 mutation (38.7%). In two cases the mutation was present in only one part of the tumour. 10 cases showed EGFR exons 19 deletions and one case with the mutation present in only one of the patterns showed synchronous exon 19 deletions and exon 21 point mutations. Of the 14 cases with EGFR mutations 10 cases were FISH positive (71%). KRAS mutations were identified in 5 cases (10%), one coexisting with EGFR ex21 point mutation. All cases were HER2 wild-type. 8 cases with EGFR mutations demonstrated EGFR protein expression and 6 cases were negative. EGFR mutational status and FISH results showed a moderate agreement/concordance. Concordance between EGFR FISH results and mutational status with EGFR IHC expression was fair. Frequently, when a mutation is identified it is present in all the patterns of 1 adenocarcinomas. Mutations of HER2 do not seem to be important in lung adenocarcinomas pathology. KRAS and EGFR mutations are in general mutually exclusive, but in rare cases they may coexist.

P447
Genetic analysis of two novel mucin-like genes in the disease-susceptibility locus for diffuse panbronchiolitis
Minako Hjikata1, Ikumi Matsuhashi1, Hideyuki Ito1, Jun Ohashi1, Sakae Homma1, Yoshio Taguchi1, Atsuko Azuma2, Shoji Kudoh2, Naoto Kiechi2, Department of Respiratory Diseases, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan; 1Department of Thoracic Surgery, National Institute of Public Health and Medicine, Tokyo, Japan; 1Department of Respiratory Medicine, Toki University School of Medicine, Tokyo, Japan; 1Department of Respiratory Medicine, Teur Hospital, Nara, Japan; 1Division of Pulmonary Medicine, Nippon Medical School, Tokyo, Japan; 1President, Fujajuku Hospital, Tokyo, Japan

Background: Diffuse panbronchiolitis (DPB), which is characterized by chronic inflammation in respiratory bronchioles and sinusbronchial infection, is a common genetic disease affecting East Asians. DPB is strongly associated with HLA-B54 in Japanese and HLA-A11 in Koreans. We hypothesized that a major susceptibility gene for DPB might be located between the HLA-A and HLA-B loci and recently cloned two novel mucin-like genes designated panbronchiolitis related mucin-like 1 and 2 (PBMUCL1 and PBMUCL2) in the candidate region. We found disease-associated genetic polymorphisms in the new genes.

Results: Linkage analysis in two large families complicated with PA VM revealed a linkage to the HHT1 locus (encoding endoglin; ENG). Three novel mutations were found in four families, all of which led to a frame shift: a G to C transversion at the splicing donor site of intron 3 (In3+1 G>C) in one family, one base pair insertion (A) at nucleotide 828 (exon 7) of the endoglin cDNA in two large families (a282-29 ins A), and a four base pair deletion (AAAAG) beginning with nucleotide 1120 (exon 8) of the endoglin cDNA (c.1120-1123 delAAAAG) in one family. The insertion of A in exon11 (c.1470-1471 insA) mutation was found in one family.

Summary and conclusion: The population prevalence of HHT in the country is estimated to be 1:8,000 - 1:5,000, roughly comparable with those reported in European and U.S. populations, which is contradictory to the traditional view that HHT is rare among Asians. We recommend that families with HHT be screened for gene mutations in order that high-risk individuals complicated with PA VM receive early diagnosis and treatment initiation that will substantially alter their clinical course and prognosis.

P448
Genetic epidemiology of hereditary hemorrhagic telangiectasia complicated with pulmonary arteriovenous malformation
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P449
Genetic polymorphisms in TNF genes and tuberculosis in cystic fibrosis patients
Galinha Scharmin2,1, Alexander Pukhalovsky3,1, Nikolai Kapranov3,1, Vladimir Alesikhin2,1, 1Department of Cystic Fibrosis, Research Centre for Medical Genetics, Moscow, Russian Federation; 2Laboratory of Cytokines, G.N. Gabrielevich Institute of Epidemiology and Microbiology, Moscow, Russian Federation

The genes for tumor necrosis factor-a (TNF-a; TNF) and lymphotixin-a (LT-a; LTA) are arranged in tandem within MHC III region of chromosome 6 in the same transcriptional orientation. This formation is conserved, even in marupsulps, suggesting that there may be some functional advantage to this arrangement. The proteins encoded by TNF and LTA are known to interact as complementary factors in various cell signaling networks. Single nucleotide polymorphism sites for TNF (308 G>A) and LTA (252 G>A, 252 C>G) were investigated with TagMan allelic discrimination assay. 150 cystic fibrosis (CF) subjects were enrolled into the study. The distribution of allelic variants of TNF and LTA genes in CF patients did not differ from those in health subjects of Moscow and European populations. We did not find any association between TNF or LTA genotypes and CF lung disease progression. In the same time the carriers of -308A allele more frequently had asthma and other atopic disorders as compared to patients homozygous for -308G allele (14.9 vs 5.3%, p< 0.05). There was no correlation of tuberculosis among patients with 252G alleles. In the same time in 7.9% of 252G/A carriers tuberculosis infection was documented (p<0.03). Besides, the subjects with genotype 252A/2 demonstrated a significant elevation of plasma TGF-β1 in comparison with carriers of 252G allele (72.6 vs 32.4 pg/ml; p< 0.05). Our data confirm the clinical importance of -308 A TNF allele for asthma development and provide robust evidence that LTA gene variants are involved in tuberculosis etiology.

73. Pleural diseases and pneumothorax

P450
Value of the video assisted thoracoscopy in the diagnosis of the pleural effusions – Our experience
Cornel Savu1, Cornel Petreanu1, Vasile Grigore1, Nicolae Galie1, Emilie Tabacu2, 1Clinic of Thoracic Surgery, National Institute of Pneumonology and Tuberculosis Prof. Dr. Marius Nasta, Bucharest, Romania; 2Clinic of Pneumonology, National Institute of Pneumonology Prof. Dr. Marius Nasta, Bucharest, Romania

Introduction: Pleural effusions are a common and significant clinical problem.
The diagnosis required sometimes the practice of the thoracotomy to biopsy the pathological pleura. Also, this method is utilized in treatment of different effusions like debridement of the empyema, pleurodesis in the malignant effusions. Also, it permits to establish if an effusion pleural is neoplastic or paraneoplastic, with consequence of the surgical treatment.

Material and method: The work presents our experience with this method in the last two years. We retrospectively reviewed 131 patients (82 males, 49 females, mean age: 62 years). The indications of videoassisted thoracotomy are presented in table no.1 and 2.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>31</td>
<td>32.97%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>15</td>
<td>15.95%</td>
</tr>
<tr>
<td>Colonic cancer</td>
<td>7</td>
<td>7.44%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>16</td>
<td>17.02%</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>15</td>
<td>15.95%</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>5.31%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary fibrous tumor of the pleura</td>
<td>2</td>
<td>5.40%</td>
</tr>
<tr>
<td>Pleural tuberculosis</td>
<td>19</td>
<td>51.55%</td>
</tr>
<tr>
<td>Tuberculous infection</td>
<td>11</td>
<td>29.22%</td>
</tr>
<tr>
<td>Associated atelectasis</td>
<td>3</td>
<td>8.01%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2</td>
<td>5.40%</td>
</tr>
</tbody>
</table>

Additional, we performed a minithoracotomy or thoracotomy for 26 cases. Mean period of hospitalization was 4.2 days.

Results: The benefits of this method are obvious, with hospitalization cost smaller and with discharge of the patient faster.

Conclusions: The videoassisted thoracotomy is an indispensable method of diagnosis of pleural effusions.

P451

Tuberculous empyema thoracis surgical perspective. A tertiary care center experience

Methods: Surgical treatment.
The degree of chronic pleural effusions and the choice of the optimal method of treatment of pleural effusions, pleural thickening, the higher number and bigger size of air inclusions (flushing gas bubbles). The value of the mean of pleural content increased to +35 HU.

Results: All patients of the first group had thoracoscopic surgical treatment.
The patients of the second group were operated on by open decortication.

Conclusions: 1. Computer tomography provides the opportunity to differentiate accurately enough the density of the pleural content and evaluate it in Hounsfield units.
2. Preoperative assessment of the nature of pleural content gives the opportunity of choice of surgical intervention, adequate to the nature of the inflammatory process.

P452

Significance of computed tomography in diagnostic of pleural content and the choice of the method of surgical treatment
Marina Rusetckaya, Vladimir Petukhov.

Introduction: The authors have aimed at stating more precisely the value of Hounsfield units used for computed tomography in case of acute, subacute and chronic empyema, comparing these data with the results of morphologic investigation of operation material.

Goal of work: To evaluate the possibility of beam diagnostics for determining the degree of chronic pleural effusions and the choice of the optimal method of surgical treatment.

Methods: Case histories of 40 patients with pleural effusions treated at the thoracic department of Vitebsk Regional Hospital. All patients were divided into two groups.

Results: On the scans of the first group patients there was the content of the pleural cavity with slightly irregular contours, areas of gas, pleural thickening (mesh structure), the mean attenuation of effusion ranged from +13 HU up to +27 HU due to the liquid, gas and organized components.

P453

Lung and breast cancers are the most common causes. Severe cases can present background: Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis but other species of Mycobacteria are also present which may produce similar change. A granulomatous response associated with intense tissue inflammation and damage, and is a leading pulmonary disease whereas pleural tuberculosis is the most common form of extra-pulmonary Tuberculosis. 90% originates from primary infection, while 10% due to reactivation of cavitated or fibrocaceous lesion.

Patients and methods: Between June 2008 to June 2009, 85 patients of 20-50 years of age underwent Thoracotomy and decortication for Tuberculous Empyema Thoracis were included in this study. Age less than 30yrs and above 50yrs, poor functional and nutritionally status, underlying parenchymal disease, A.T.T. Defaulter and MDR T.B were excluded.

Results: There was no mortality, mean day of discharge was 6 post-operative date 5/85 had wound complications, 3 patients required upto 10 day of hospitalization due to air leaks and wound complications 1 patient required revision of procedure and ended with pleurocutaneous window. Operating patients early with T.B Empyema Thoracis carries equally good results if compared to those operated at a later stage.

Conclusion: Operating patients early with T.B Empyema Thoracis carries similar results if compared to those operated at a later stage. Patient selection are an important factor. Key to success is: Patients taking adequate dose of A.T.T. Observed Treatment with regular followup. Surgery remains the standard Treatment.

P454

Analysis of lung function test at patients with pleural empyema treated with thoracotomy and decortications
Goran Kondov, Kisto Colanceski, Zoran Spirovski, Saso Jovev.

Material and methods: We analyze lung function at 18 patients surgically treated in last 3 years which was followed at least 6 months.

Results: Expected mean VC was 4650 ml, and expected mean FEV1 was 3450 ml.

– Realized mean VC was 2850 ml, and realized mean FEV1 was 1750 ml.
– Mean VC after 3 months after surgery as 3430 ml, and mean FEV1 was 1700 ml.
– Mean VC after 6 months after surgery as 2850 ml, and mean FEV1 was 1700 ml.

Discusion: Early detection and treatment of empyema is essential in treatment of empyema, where use of thoracic drainage with or without streptokinase or use of VATS decortications were methods of choice in treatment.

Conclusion: Thoracotomy with decortication is the only solution of treatment of fibronodular pleural empyema, where trapped lung was very often detected.

P455

Malignant pericardial effusion and pericardial- peritoneal window
Catarina Guimaraes, Claudia Lares Santos, António Correia de Matos, Ana Figueiredo, Fernando Barata.

Background: The metastatic pericarditis is a rare complication of advanced cancer. Lung and breast cancers are the most common causes. Severe cases can present significant symptoms.
with cardiac tamponade and shock, and pericardioedema is usually the initial approach. However the effusion may rapidly re-accumulate and a surgical decompression, as pericardio-pleural window (PPW), has proved to be effective with a consequent symptom relief and a better quality of life.

Objectives: Characterize patients with malignant pericardial effusion (PE). Evaluate the role that PPW plays in the management of PE. Determine median survival of patients after this procedure.

Material & methods: Retrospective review of the patients undergoing PPW from 1998 through 2010. Results: 92 patients underwent 24 PPW, with a mean age of 52.2 years old, and 71.1% were male. Lung cancer was the cause in 75% at the time of the cancer diagnosis PE was present in 38% of patients. In the other patients there was an average of 103 weeks (after the diagnosis) to occur PE of which 35% of cases were undergoing chemotherapy. The majority (70.8%) had also pleural effusion. In 70.6% of patients were performed at least one pericardiocentesis before the PPW, with a mean fluid volume of 740 ml. Two patients developed recurrent PE during follow-up. The procedure was well tolerated, with a median survival after the procedure of 11 weeks. No patient developed peritoneal carcinomatosis and no deaths were related to the procedure.

Results: Lung cancer was the most frequent cause undergoing PPW. This surgical decompensation is a simple, safe, and an effective method of palliation patients with malignant PE. Median survival rate after performing the procedure was low.

P456 Thoracic empyema: Medical and surgical treatment
Inês Ladeira, Carla Ribeiro, Maria Brito, Teresa Shiang, Pneumology, Centro Hospitalar Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal

Introduction: Thoracic empyema is the presence of pus in the pleural cavity. Mostly it complicates cases of pneumonia, trauma or is iatrogenic.

Initial approach includes chest drain and empirical antibiotic therapy. The use of fibrinolytics is controversial, according to the experience of each center. Current surgical options include thoracotomy (VATS) or thoracotomy. Mortality rate is up to 24%.

Methods: Review of medical records of patients admitted from 2006 to 2010 with diagnosis thoracic empyema.

Results: 44 patients had thoracic empyema, mean age 60.5 years, 70% male; 75% had infectious causes (pneumonia-68%), chest trauma 7% and 18% iatrogenic. Microbiology was isolated in 25%.

30 patients used medical therapy only; 6. Fibrinolytics were not used.

14 patients underwent surgical treatment (1 VATS and 13 thoracotomy), 78.6% men, mean age 53.3 years, 57% related to infection, 29% iatrogenic and 14% trauma. The mean hospital stay period was 26 (23-31) days and a shorter period of chest drain tube (17 vs 20 days) but there were no differences between co-morbidities, pleural effusion volume, isolated bacteria or antibiotic therapy.

Conclusions: As expected, empyemas mainly complicated infections.

Patients were younger in the operated group, associated to more cases of trauma or iatrogenic empyemas, but there were no other differences between groups. Thoracotomy was the principal method of surgical treatment. Since there was only 1 VATS we can’t compare the efficacy and complications of both surgical approaches, although it’s use is increasing in many centers. Surgical approach should be considered early to reduce hospitalization time and improve outcome. Mortality rate was between expected values and related to patient’s co-morbidities.

P457 Fibrous cavernous pulmonary tuberculosis (FCT) complicated by spontaneous pneumothorax (SP) Kazim Mukhamedov, Avazbek Murzabekov, Seralri Massavirov, Fazlal Ismailova, Nurali Djurayev, Faculty of Pathology, Tashkent Medical Academy, Tashkent, Uzbekistan

We undertook the treatment of SP clinical course that complicated FCT to 233 patients. Men were 205, women were 17 at the age 18-72 yr. 121 patients had infected pleural effusion, 31 from other TB clinics, 18 from general medical network, (GMN), 37 from peniintary system, 15 went to clinics themselves. Duration of tuberculosis (TB) fluctuated from 1 year to 16 years. MBT were revealed in 90.6% patients. 33 patients were admitted to clinic within 1-7 days with onset of SP process, 190 patients in more late terms (from 15 days to more than 1 month). Before admitting to clinic 134 patients had been made punctures and drainage of pleural cavity. (PC). 139 patients were admitted with complicated pleura empyema, 84- had a mild favorable SP process. The treatment started with puncture and drainage of PC. Polychemotherapy was made in standard regime and by broad-spectrum antibiotics when indicated as well as correction of dysproteinemia and hypotinuminous, oxygen-soda and tonic condition. Surgically approaches were used just in 5 patients with good effect. Segmental pulmonary resection was performed to 1, pneumectomy-1, bullectomy-1, and pleurectomy-2. Clinical convalescence was reached in 32, improvement in 86, no changes in 46, and death recorded in 3. Lethality was in 25, 1% cases.

Conclusion: SP problem under FCT is urgent. The search of new ways for more effective diagnostics and treatment to this severe group of patients is needed. At present time, the causes of poor surgical activity are mostly related with large spread and TB process activity, of phthisiourges and anesthesiologists being overcareful and lack of qualification as well as good equipment of surgical services.

P458 Do we follow the national guidelines for ICD (intercostal chest drain) insertion: A study in a district general hospital (DGH) in East of England
Vena Sireru, Y. Howe, K. Fulton, Subham Dharun, Respiratory Medicine, Queen Elizabeth Hospital, Kings Lynn, United Kingdom

AIM: To determine the compliance of ICD insertion in accordance with 2003 British Thoracic Society (BTS) guidelines.

Methodology: Retrospective analysis of all the ICDs inserted from Oct 09 to Oct 10 at a DGH in Norfolk, UK. We analysed the indications, seniority of the person performing the procedure, consent obtained, anaglasis and complications encountered.

Results: 28 Patients underwent ICD insertion. The indication for ICD insertion was non malignant effusion in 43% (12), pneumothorax in 32% (9) and malignant pleural effusion in 25% (7). The ICD was performed by SpR in 36% (10),SHO in 26% (8) and FIn 36% (10). Consent was obtained verbally in 47% (13), in writing in 32% (9) and not recorded in 21% (6). Ultrasound guidance was utilized in choosing the site of insertion in only 21% (6). All the patients 100% (28) had check CXR done following the ICD insertion. 75% (21) of the patients were given procedure analgesia.The ICDs were complicated by surgical empysemia in 11% (3) and pneumothorax in 11% (3). ICD was reinserted in 18% (5) as the tube fell out accidentally. No major complications of ICD were encountered.

Conclusion: BTS standards were achieved suboptimally in obtaining the written consent and poor in utilization of ultrasound for ICD insertion. Most of the ICDs were inserted by the seniors or under their supervision therefore we proved the complication rate is lower and in accordance with the BTS standards. Education of the 4 guidelines to the junior staff and utilization of ultrasound will improve the safety of the procedure. We will reaudit after increasing the usage of the ultrasound for ICD insertion hoping to find better results.

P459 Outpatient management of primary spontaneous pneumothorax using small-bore catheter: A prospective study
Massongo Massongo1, Bachar Chahine2, Charles Hugo Marquette3, Arnaud Scherpenber2
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The various guidelines published about the management of primary spontaneous pneumothorax (PSP), have raised up discrepancies regarding indications and methods of air removal.

We aimed to assess the feasibility of a single system small-bore drain based management of primary spontaneous pneumothorax. The end-point was 1-week success rate, secondary ones were the part of full outpatient management, the 1-year recurrence rate, the length of hospitalization stay, the cost and the side-effects.

125 patients aged > 16 years with 1st episode of PSP, were managed in the emergency room (ER) by observation alone or insertion of an 8.5 Fr "pigtial" drain, according to the experience of each center. The drain was connected to a one-way Heimlich valve. Patients were re-assessed at the 4th hour for potential admission or discharge. Patients still having air leak at day-4 were referred for video-assisted thoracocopy (VATS).

On the 60 patients recruited, 80% underwent drainage and 60% were discharged after 4 hours. Success rate was 83% at day-7, the 17% left underwent a VATS. Fifty per cent of the patients benefited from strict outpatient management and 2 procedure-related complications occurred. The length of hospitalization was 2.3±4.3 days, the 1-year recurrence rate was 17%. The financial gain of this PSP management was 1,791 to 3,940 Euros/patient/episode, compared with a manual aspiration (MA) or conventional chest tube drainage (CTD).

This one-system management offers good efficacy, safety, comfort and aesthetics; it is time and cost-effective. Our results suggest its use in a larger population, but a randomised controlled study comparing it with MA and/or CTD is needed for validation.

P460 Primary spontaneous pneumothorax size: Comparison of international guidelines
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Background: Size estimation is central to decisions on management of Primary Spontaneous Pneumothorax (PSP). International guidelines exhibit a lack of consensus on PSP sizing. We aimed to study PSP size using established techniques (Rhea, Collins and Light) and compare size classification and suggested management of American (ACCP), Belgian (BSP) and British (BTS) guidelines.

Methods: Retrospective cohort study of all patients admitted with PSP to two centres in our institution between January 2007 and July 2010. Initial inspiratory chest x-rays (digital images with size calibration) were reviewed to quantify PSP size using BTS, ACCP, BSP, Collins, Rhea and Light’s methods. Data was analysed using descriptive statistics with kappa analysis for agreement between guidelines.

Results: 105 patients were studied, median age 21 years, 72% male. Median PSP size was 58% (Collins’ method), 39% (Rhea) and 51% (Light). BTS classification
defined 56% PSPs as large compared to 72% (BSP) and 78% (ACCP). Agreement between the three guidelines was poor. There was no consensus on the influence of different surgical treatment of spontaneous pneumothorax on the lung function. Some studies confirm positive long-term effect of pleurectomy and wedge resection on the lung function.

Aim: To study the influence of different surgical treatment of spontaneous pneumothorax on the lung function. Some studies confirm positive long-term effect of pleurectomy and wedge resection on the lung function.

Methods: We aimed to see if LVRS improves CI in patients with COPD by evaluating the change in perfusion patterns and its correlation to clinical outcome after LVRS. All patients underwent LVRS at Columbia University Medical Center (CUMC) between January 1998 to October 2009. There was a significant correlation between the bilateral preoperative heterogeneity index and the postoperative 6 MWD (r = 0.400, p = 0.028). Patients showing an improvement in 6 MWD (n=13) had significantly higher post-operative heterogeneity index as compared to the ones failing to show functional improvement in 6 MWD (r = 0.233 ± 0.28 vs. 2.25 ± 0.55, p = 0.025).

Conclusion: Lung SPECT perfusions pattern correlates with the clinical improvement and warrants evaluation as a pre-operative assessment tool in patients with COPD undergoing LVRS.

P465
Does lung volume reduction surgery improve chronotropic incompetence in chronic obstructive pulmonary disease (COPD) patients?

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Introduction: Chronotropic Incompetence (CI), or an attenuated heart rate (HR) response to exercise, has been widely established as a predictor of mortality in patients with COPD. LVRS is known to improve morbidity and survival in patients with COPD.

Objectives: We aimed to see if LVRS improves CI in patients with COPD by evaluating CI in maximal exercise testing before and after LVRS.

Methods: A retrospective chart review was performed on 82 patients who had undergone LVRS at Columbia University Medical Center (CUMC) between January 1998 to October 2009. There was a significant correlation between the bilateral preoperative heterogeneity index and the postoperative 6 MWD (r = 0.400, p = 0.028). Patients showing an improvement in 6 MWD (n=13) had significantly higher post-operative heterogeneity index as compared to the ones failing to show functional improvement in 6 MWD (r = 0.233 ± 0.28 vs. 2.25 ± 0.55, p = 0.025).

Conclusion: CI is very abnormal in patients with severe COPD before LVRS and is improved after surgery. This improvement is in agreement with the observed increase in exercise capacity and improvement in PFT. The mechanism of the improvement in CI is not clear, but may be related to the improvement in pulmonary mechanics seen after successful LVRS. Further investigation into the implications of this change in CI is needed.

P466
Ultrasound guided pleural aspiration and chest drain insertion – A prospective study

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Pleuritic aspiration and chest drain insertion are important procedures required in the management of pleural disease. Small bore chest drain insertion using the Seldinger technique is assumed to be safer and better tolerated. However, there is no data to support this and incidents of serious complications have been reported. As a result, the British Thoracic Society recommend thoracic ultrasound (TUS) for pleural procedures. Currently, TUS is commonly being used by respiratory physicians to identify a safe site for various interventional procedures. The aim of this study was to review the complications of ultrasound guided pleural aspiration and chest drain insertion.

Method: Data from TUS guided pleural aspirations and chest drains was collected prospectively. Complications and pain perceived by the patient was recorded on a 100mm Visual Analogue Scale (VAS, 0=no pain, 100=worst pain ever). There were 58 pleural procedures were performed: 34 (59%) pleural aspirations, 20 (34%) chest drains. 3 (5%) showed a small pleural effusion on TUS and were not suitable for a pleural procedure. Other than 1 patient having a vasovagal episode during the ultrasound procedure, there were no immediate and direct complications associated with the pleural aspirations and chest drain insertion. All chest drains inserted were 12F and all required one attempt. Mean VAS for pain during chest drain insertion was 20 (range 0–80).

Conclusion: Ultrasound guided pleural aspiration and chest drain insertion which may result in serious harm and even death is reduced by TUS guidance. TUS is commonly being used by respiratory physicians to identify a safe site for various interventional procedures. The aim of this study was to review the complications of ultrasound guided pleural aspiration and chest drain insertion.
74. Biomarkers of allergic inflammation

P467 Atopy is a risk factor for COPD symptoms: Results from the EUROSCOP study

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Background: Pathogenesis of COPD is complex and remains poorly understood. EUROSCOP (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) showed that 18% of their COPD participants were atopic (Watson, L. et al. ERJ 2006; 28:311-8).

We investigated whether atopy affects symptoms and lung function in these COPD patients.

Methods: We included 843 male and 320 female smokers with mild to moderate COPD from EUROSCOP. Risk factors associated with the presence of atopy (positive phadiatop) as well as the association between atopy and symptoms, and atopy and lung function (FEV1 and FVC) were analysed using multiple regression models adjusted for confounders. Interactions between atopy and gender, age, and smoking were also investigated.

Results: Prevalence of atopy was higher in males than females (21% vs 10%, p<0.001). Male gender (OR: 2.20; 95% CI: 1.47-3.36), BMI (1.04; 1.00-1.08) and age (0.97; 0.95-0.99) were associated with atopy. Additionally atopy was associated with a higher prevalence of cough (1.71; 1.26-2.34) and phlegm production (1.50; 1.10-2.03) in the total population, and with waking up with chest tightness in females (2.69; 1.11-6.55), male: 0.84; 0.47-1.49, female vs male: 3.21; 1.12-9.25). There were no significant interactions between atopy and age or smoking with respect to symptoms. Atopy was not associated with lung function.

Conclusions: The present study for the first time shows that atopic COPD patients may more likely report respiratory symptoms than non-atopic COPD patients. However, atopy is not associated with lung function. Of interest, male gender, higher BMI and younger age are risk factors for atopy in COPD patients. Study was supported by AstraZeneca.

P468 Granulyme B expression in lung of fatal asthmatics

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Introduction: Granulymes are serine proteases mainly produced by CD8 and NK cells, and are involved in the pathogenesis of many inflammatory disorders. Granulyme B (GzmB) is released towards target cells and can also be released non-specifically and is of cleaving extracellular matrix (ECM) components contributing to ECM degradation and remodeling in chronic inflammation. Recent studies have also shown participation of GzmB in allergic inflammation, but there are no descriptions of the its expression in fatal asthma.

Methods: We studied large and small airways and lung parenchyma of 12 patients that died of fatal asthma (FA) and 8 controls (CTR). Using image analysis we measured the number of GzmB positive cells in the inner layer (IL), smooth muscle (SM) and outer layer (OL) of both large (LA) and small airways (SA) and in peribroncholar (PS) and distal (DS) alveolar septa. Values (median [IQR]) were expressed as GzmB+ cells/BS length (cells/mm) in OL and IL. GzmB+ cells/SM area (cells/mm2) in SM, and as GzmB+ cells/segmental length (cells/mm) in PS and DS.

Results: In LA we found a higher number of GzmB+ cells in IL [FA=12.9 (5.1), CTR=5.8 (3.1), p=0.002] and OL ([FA]=27.2 (9.3), CTR=7.5 (2.4), p=0.001) in FA, but no differences were observed in SM. In SA, the number of GzmB+ cells was also higher in IL [FA=8.3 (4.9), CTR=2.8 (2.1), p=0.03] and OL [FA=15.9 (10.24), CTR=0.9 (0.9), p=0.03] in FA, but no differences were observed in SM.

Conclusions: The results show that GzmB expression is increased in FA and may contribute to the previously described process of airway remodeling in these patients.

P469 Differences in responsiveness of blood neutrophils for IL-8 to identify two distinct groups of COPD patients

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In COPD severity of disease is generally diagnosed by the GOLD guidelines. The GOLD stages, however, poorly correlate with disease progression. The extend of systemic inflammation in COPD patients plays a role in the progression of the disease. Therefore, the severity of the systemic inflammatory response of COPD patients was characterized by phenotype analysis. Two distinct groups of COPD patients were identified by phenotypic characteristics.

In COPD severity of disease is generally diagnosed by the GOLD guidelines. The GOLD stages, however, poorly correlate with disease progression. The extend of systemic inflammation in COPD patients plays a role in the progression of the disease. Therefore, the severity of the systemic inflammatory response of COPD patients was characterized by phenotype analysis. Two distinct groups of COPD patients were identified by phenotype analysis. In the study, expression of activation epitopes on neutrophils was analyzed by flow cytometry. Responsiveness for IL-8 was measured by analysis of cells in the presence or absence of IL-8.

Responsiveness of neutrophils for IL-8 was measured by the ratio of CD11b in the presence and absence of IL-8, identified two distinct COPD patient populations. Population 1 (55%) was comparable to the healthy smokers and phenotype II (45%), showed a significantly higher mean ratio of 17.74 ± 0.78 vs. 5.6±0.53, respectively. These two groups did not differ in FVC1, but a higher expression of CD11b was found in group 2 (p=0.001) in FA, but no differences were observed in SM.

Conclusions: The results show that GzmB expression is increased in FA and may contribute to the previously described process of airway remodeling in these patients.

P470 A decreased integrin Mac-1 (CD11b/CD18) induced respiratory burst in neutrophils of COPD patients

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Introduction: Neutrophils of COPD patients are characterized by changes in activation of the respiratory burst. The aim of this study was to investigate the control of the respiratory burst in neutrophils of COPD patients upon engagement by platelet-activating factor. The ROS production in neutrophils of COPD patients exhibited a primed phenotype in the context of IL-8. To our surprise
P471

IL-18 in infectious exacerbations of COPD

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The innate immune system is critical in recognizing bacterial and viral infections to evoke a proper immune response. IL-18, a pro-inflammatory and pro-apoptotic cytokine with crucial role in host defense against bacterial invasion is increased in lungs, serum and sputum of COPD patients, suggesting that IL-18 may be involved in chronic inflammation of COPD. We aimed to investigate the effect of infectious acute exacerbations of COPD (AECOPD) on IL-18 levels.

We examined 40 patients with COPD hospitalized for infectious AECOPD according to Athonson's criteria and 20 patients with stable COPD. We examined sputum for inflammation and for bacterial infection using PCR. IL-18 was measured in induced sputum and serum at baseline and after treatment of the exacerbation. Immunocytochemistry of IL-18 expression in sputum cells was performed using a monoclonal IL-18 antibody.

All patients had no previous hospitalization the preceding 3 months and none was diagnosed with pneumonia. IL-18 levels in sputum were found significantly lower in AECOPD compared to stable state (p=0.05), while right after treatment IL-18 levels were increased compared to stable state levels (p<0.05). Positive staining of IL-18 was observed in macrophages in immunocytochemistry. An inverse correlation was found between IL-18 levels and sputum macrophages in AECOPD (r=-0.30, p=0.026). Serum IL-18 levels were elevated in exacerbations (p<0.05) compared to stable state, and decreased after treatment to stable disease levels (p<0.05). Our data show that although IL-18 is involved in host defense against bacterial pathogens in infectious AECOPD there may be a dysregulated activation of airways' macrophages and perhaps inflammation mediated pathways.

P472

Serum and nasal lavage fluid Clara cell protein in children with allergic rhinitis

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Background: Allergic rhinitis is the most common chronic disorders of childhood with prevalence of up to 40% in children. Clara cell secretory protein (CCSP) is secreted by Clara cells in the lining fluid of airways. It has an immune-modulatory and anti-inflammatory activity.

Aim of work: Study aimed at evaluating Clara cell secretory protein as a pneumocyte biomarker in serum and nasal lavage fluid of children with allergic rhinitis.

Methods: A cross sectional case-control study was conducted on sera and nasal lavage fluid samples from 15 children with allergic rhinitis, recruited from Children’s hospital, Ain Shams University, and 15 healthy children as a control group.

Results: Children with allergic rhinitis had a male to female ratio 2 to 1, with a mean age of 9.47 ±2.28 years. Rhinitis and nasal obstruction were the most frequent symptoms (100%) followed by itching (93.3%) then sneezing (73.3%). Serum CCSP mean±SD was 2.03±0.59 ng/ml; it was reliable to predict allergic rhinitis (p<0.0001); while nasal lavage CCSP mean±SD was 12.73±8.25 ng/ml and it was not reliable to predict allergic rhinitis. The best cut-off value was 3.75 μg/l with a sensitivity of 100%, specificity 80%, with a diagnostic accuracy of 90%.

Conclusion: In conclusion, Clara cell secretory protein is a new peripheral sensitive marker of airway injury allowing researchers to evaluate the integrity of the air blood barrier. Furthermore, serum CCSP level is a non-invasive predictor of allergic rhinitis but not nasal lavage fluid CCSP.

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Elevated CEA levels in sera in patients with allergic bronchopulmonary aspergillosis (ABPA)

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Background: ABPA is an allergic disease associated with peripheral blood eosinophilia and elevated total IgE in serum. It sometimes accompanies with bronchiectasis filled with mucus plug detected by chest X-ray or CT films or fibrotic bronchoclasus. Mucus plug is not infrequently misdiagnosed as lung tumor. Carcinoembryonic antigen (CEA) is one of tumor markers and measured as a diagnostic as well as surrogate marker of bronchogenic carcinoma. It has been reported that some patients with ABPA demonstrated elevated CEA levels in their sera.

Aim: To evaluate clinical significance of serum CEA level in patients with ABPA.

Methods: Ten patients (6 women), aged from 39 to 78 (median; 67) with ABPA were evaluated. All patients were never smokers or ex-smokers. Serum CEA level, eosinophil number, total IgE, Aspergillus fumigatus (Af)-specific IgE- and precipitating antibodies were measured. Chest roentgenogram and or CT were examined when blood test was performed. For comparison, serum CEA levels were also evaluated in patients with bronchiectasis (n=20).

Results: Among 10 patients with ABPA, five demonstrated elevated serum CEA levels (6.2 – 140.0 ng/ml; normal range ≤ 5 ng/ml). Massive mucus plugs were demonstrated in four out of five patients on chest CT or X-ray films. Two out of five patients were treated with systemic glycerocorticosteroids resulting in the decrease in CEA levels. Another patient showed the decrease in CEA spontaneously in parallel with the decrease in eosinophil number.

Conclusion: Massive mucus plug may induce CEA synthesis from airway epithelial cells lining on the ecatasis.
P476
Is analysis of exhaled breath condensate equivalent to that of bronchoalveolar lavage fluid (BALF)?
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Background: Although the analysis of bronchoalveolar lavage fluid (BALF) is the most useful examination for the assessment of airway inflammatory markers, it is an invasive technique with limitations and risks for side effects.

Aims: The aim of this study was to examine the molecules included in exhaled breath condensate (EBC) in comparison with BALF, and to clarify the clinical usability of EBC.

Methods: EBC was collected from sixteen subjects suspected to have sarcoidosis just before BAL. The 40 different inflammatory molecules in EBC and BALF were analyzed with a protein array method.

Results: BALF levels of 6 inflammatory molecules including soluble tumor necrosis factor receptor type II (sTNF-R111) and regulated upon activation, normal T cell expressed and secreted (RANTES) were significantly correlated with the percentage of lymphocyte in BALF (%Lym). EBC levels of 13 inflammatory molecules including sTNF-R111 and RANTES were significantly correlated with %Lym. We found significant correlations between the levels of EBC and BALF in 16 out of 40 inflammatory molecules. Levels of macrophage colony-stimulating factor (M-CSF), RANTES, TNF-α, and sTNF-R111 in EBC were significantly correlated with those in BALF. Their levels in EBC were also significantly correlated with %Lym.

Conclusion: Highly sensitive approach to protein array in EBC allowed us to detect inflammatory molecules. Comprehensive analysis of EBC might be equivalent to that of BALF.

P477
Expression of galectins in asthma patients
Silvia Sánchez-Cuéllar1, Hortensia de La Fuente 2, Amalia Lamana 2

Subjects (N: w/m) Asthma (24: 19/5) Controls (18: 8/9)

Clinical characteristics

<table>
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<tr>
<th></th>
<th>Mean (Range)</th>
<th>Mean (Range)</th>
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<tr>
<td>Age (range)</td>
<td>50.34 (24–75)</td>
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<td>ICS BDP dose &lt;500/500–1000/1000 mg/day (n)</td>
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<td>Lung Function:</td>
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<tr>
<td>FEV1 (%) pred (nl)</td>
<td>94.5 (2623)</td>
<td>105.8 (1037)</td>
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<td>FVC (%) pred (nl)</td>
<td>100.4 (1220)</td>
<td>108.5 (2478)</td>
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<tr>
<td>FEV1/FVC ratio</td>
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<td>Differential cell count in induced sputum:</td>
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<tr>
<td>Total cells (105)</td>
<td>4.7 (1–20)</td>
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<td>Macrophages (%)</td>
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<tr>
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<td>3.85 (2.5–7.3)</td>
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<tr>
<td>ACS (%)</td>
<td>22 (16–25)</td>
<td>25</td>
</tr>
<tr>
<td>Current smokers (%) (/YN)</td>
<td>8.3% (2/22)</td>
<td>44% (8/18)</td>
</tr>
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Results: Gal-1 and gal-3 mRNA levels in asthma patients (mean±SEM= 2.6±4.0, and 4.4±1.4, respectively) were lower than in healthy subjects (4.7±1.2, and 20.0±8.7). Gal-9 mRNA expression did not vary significantly between the two groups (3.2±1.3 vs 3±1.1). Asthma patients contained elevated mRNA levels of IL-5 and IL-13 (p<0.05).

Conclusions: The low levels of the negative regulator of galectins in human asthma may contribute to the inflammatory response present in this disease.

P478
Analysis of IgE and C-reactive protein as possible predictors of exacerbation patients with asthma
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Aim: To study correlation of IgE level and C-reactive protein (CRP) for exacerbation of the disease in asthmatic patients.

Methods: Asthmatic subject were examined for achieving of asthma control according to GINA recommendation. Numbers of exacerbation of asthma during one month were analyzed. The patients were followed in six month period (since first January to 30th of Jun. Average monthly days of exacerbations was calculated. IgE level in the blood was measured using Enzyme-linked Immunoassay (ELISA), and CRP was measured by immunoturbidimetry. Assessment of asthma control was considered using Asthma Quality of Life Questionnaire (AQLQ).

Results: The study includes 63 patients with asthma. Average level of IgE was 674 IU/mL (SD 167), range 56-3785 IU/mL, 1 IU=3.2 ng; average level of CRP was 16.4 mg/mL (SD 6.3), range 5-48; Average number of days in exacerbation during one month was 3.6 (SD 2.4), and varied from zero, patients with no exacerbation, to 21. Using test of multiple correlation it was shown statistical significant correlation (level p<0.05) between IgE and CRP from one side, and number of days with exacerbation from the other. Patients with higher level of CRP were most likely to have exacerbation, than those with higher level of IgE. AQLQ was worse in those with higher level of CRP, than in those with higher level of IgE.

Conclusion: In this study CRP was shown as stronger predictor of asthma exacerbation and worse quality of life than total IgE level in asthmatic subjects.

P479
Structure-function relationship between extracellular matrix in airway smooth muscle and dynamics of lung function in asthma
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Rationale: Asthma is characterized by an increased deposition of extracellular matrix (ECM) within the airway smooth muscle (ASM) [Panettieri 2008, Araujo 2008]. We hypothesized that ECM composition within ASM is associated with the dynamics of lung function.

Aim: To investigate the fractional areas of collagen I and III within ASM, and their association with spirometry and respiratory resistance Rrs and reactance Xrs in asthmatics and controls.

Methods: Atopic mild asthmatics (n=10, no ICS) and controls (n=17) were included in this cross-sectional study. Spirometry, PC20, Rrs and Xrs (forced oscillation technique during tidal breathing and deep inspiration) were measured. Parafilm sections from bronchial biopsies were stained for collagen I and III by immunohistochemistry, and fractional areas were obtained by image analysis. Results: There was no difference in fractional areas collagen I and III within ASM between asthmatics and controls (p<0.05). However, ASM collagen III was correlated with the change in Rrs after deep inspiration in asthmatics (p=0.74, and 0.05).

Figure 1
Symptoms of hyperresponsiveness (AHR) in young allergic subjects without respiratory symptoms

Background: The fraction of nitric oxide in exhaled air (FeNO) is increased in allergic asthma and the degree of IgE sensitisation to aeroallergens relates to FeNO levels. Local IgE-mediated sensitisation to food allergens is known to increase asthma risk, but the relation between IgE sensitisation to food allergens and FeNO has been little studied previously.

Aim: To investigate in an ongoing asthma study if the presence of food allergy influences the levels of exhaled NO and which food allergens appear to be important.

Methods: Within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS), measurements of FeNO and specific IgE (sIgE) against the allergens included in ImmunoCAP Phadiatop and f5 (Phadia Allergy, Sweden) were done in 170 patients with physician-diagnosed asthma.

Results: Asthmatic subjects with IgE sensitisation to both Aero- and food allergens (n=21) had higher PC20 levels than subjects sensitised only to aeroallergens (n=93) (21.2 ppb (18.4, 24.4) vs 15.6 ppb (13.2, 18.6), p=0.006). This difference was confirmed (p=0.03) in a multiple linear regression model after adjustments for sex, height, lung function and age. The sIgE levels to aeroallergens were higher in subjects also sensitised to food allergens (p>0.05). Peanut sensitisation was more common (63/77 subjects) and peanut FeNO levels were independently associated with increased FeNO, even after adjustment for the sum of sIgE to aeroallergens.

Conclusion: peanut sensitisation was independently associated with increased airways inflammation in allergic asthma. A possible mechanism might be a further enhanced Th2 cytokine-driven inflammation related to peanut IgE sensitisation.

P482 ADRB2, ADAM33 and AAT gene polymorphisms and IgE-mediated asthma in Russian patients

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Background: Asthma is complex disease which pathogenesis is a mix of environmental and genetic factors. A predisposition of airways to bronchoconstriction is of great interest in asthma genetics. The aim of our study was to evaluate an effect of polymorphisms ADRB2 G16Gly and Glu27Gln in beta-2-adrenergic receptor (ADRB2) gene, Glu26Val and Gln42Ile in alpha-1-antitrypsin (AAAT) gene and 5'4 in a distinserin and metalloprotease domain 33 (ADAM33) gene in predisposition to IgE-mediated asthma in Russian patients from Moscow.

Methods: 230 patients with IgE-mediated asthma and 214 healthy individuals were examined. The genotyping was performed by MALDI-TOF mass spectrometry.

Results: Allele G of ADRB2 G16Gly and allele C of Glu27Gln (both markers in ADRB2 gene) showed strong association with atopic bronchial asthma (OR = 2.51 and 1.46, respectively, p<0.05). Allele A of ADRB2 G16Gly and allele G of Glu27Gln of that gene was found to have protective effect (OR = 0.76 and 0.69, respectively, p<0.05). Additionally one of haplotypes of ADRB2 gene (A-G) also was associated with protection from asthma development (OR = 0.43, p=0.008). No association was detected between other studied SNPs and development of asthma.

Conclusion: Our results suggest that ADRB2 G16Gly and Glu27Gln polymorphisms in ADRB2 gene strongly contribute to predisposition to IgE-mediated asthma. Probably ADRB2 and AAT gene are not directly involved in predisposition to asthma and those genes possibly realize their effects when asthma is already developed.

P490 Peutant sensitisation is independently associated with increased airways inflammation in allergic asthma

Andrei Malinovschi1, Christor Janson3, Pia Kalm-Stephens2, Katarina Nisser2, Lennart Nordvall3, Kjell Alving3, 1Dept. of Medical Sciences: Clinical Physiology, Uppsala University, Uppsala, Sweden; 2Dept. of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden; 3Dept. of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden

Background: In vivo fraction of nitric oxide in exhaled air (FeNO) is increased in allergic asthma and the degree of IgE sensitisation to aeroallergens is known to increase asthma risk, but the relation between IgE sensitisation and food allergens and FeNO has been little studied previously.

Aim: To investigate in an ongoing asthma study if the presence of food allergy influences the levels of exhaled NO and which food allergens appear to be important.

Methods: Within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS), measurements of FeNO and specific IgE (sIgE) against the allergens included in ImmunoCAP Phadiatop and f5 (Phadia Allergy, Sweden) were done in 170 patients with physician-diagnosed asthma.

Results: Asthmatic subjects with IgE sensitisation to both Aero- and food allergens (n=21) had higher PC20 levels than subjects sensitised only to aeroallergens (n=93) (21.2 ppb (18.4, 24.4) vs 15.6 ppb (13.2, 18.6), p=0.006). This difference was confirmed (p=0.03) in a multiple linear regression model after adjustments for sex, height, lung function and age. The sIgE levels to aeroallergens were higher in subjects also sensitised to food allergens (p>0.05). Peanut sensitisation was more common (63/77 subjects) and peanut FeNO levels were independently associated with increased FeNO, even after adjustment for the sum of sIgE to aeroallergens.

Conclusion: Peanut sensitisation was independently associated with increased airways inflammation in allergic asthma. A possible mechanism might be a further enhanced Th2 cytokine-driven inflammation related to peanut IgE sensitisation.

75. The new clinical spectrum of lung diseases: from bronchi to pleura

P483 Different treatment courses with inhaled corticosteroids for eosinophilic bronchitis

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Background: Eosinophilic bronchitis (EB) is a common cause of chronic cough. Inhaled corticosteroids can improve sputum eosinophilia and cough severity. However, the course of treatment with inhaled corticosteroids for EB is unknown.

Objective: To observe the efficacy and recurrence in EB patients with different treatment courses of inhaled corticosteroids.

Methods: 60 patients diagnosed as EB were randomly divided into three groups with inhaled budesonide 200 μg twice daily via a turboliner for 4 weeks, 8 weeks and 16 weeks respectively. Cough severity was assessed by visual analogue scale (VAS) and daytime cough symptom score at baseline and during the treatment period. Airway inflammation was assessed by sputum eosinophil count (Eos%). All the patients were followed up for 6 months after treatment.

Results: The daytime cough score after treatment decreased in all three group (p<0.05), which was lower in 16 weeks group and 8 weeks group than 4 weeks group (p<0.05). The rate of VAS decreased over 80% after treatment were 55% in 4 weeks group, lower than 8 weeks, 16 weeks group (85%, 95%, p<0.05). The sputum eosinophilic count decreased in all three group after treatment. The rate that sputum eosinophilic count returned to normal level (Eos%<25%) was 8 weeks group (75%), 16 weeks group (95%) were significantly higher than 4 weeks group (50%, p<0.05). The rate of recurrence was 31.3%, 25.5%, 27.8% in 4, 8, 16 weeks group respectively. There are no significant difference among three groups.

Conclusion: Our results suggest that eosinophilic bronchitis should be treated with low-dose inhaled budesonide for over 8 weeks. Recurrence appear not to be related to treatment course.

P484 Impact on objective cough severity by continuous positive airway pressure (CPAP) in subjects with chronic cough and obstructive sleep apnoea – A randomized controlled trial

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Recent studies have suggested chronic cough is prevalent in patients with sleep-disordered breathing (SDB). We investigated the effect of continuous positive airway pressure (CPAP) on cough in patients with obstructive sleep apnoea (OSA) and chronic cough in a randomized controlled trial. 11 consecutive patients with OSA confirmed on polysomnography (respiratory disturbance index (RDI) >15/hour) and chronic cough >2 months were recruited. All patients underwent a CPAP titration study. 1 patient did not tolerate CPAP. 10 Patients were randomized to receive sham CPAP (4 cm H2O) or CPAP at pressures determined by the titration study for 1 month. The primary outcome was objective 24-hour cough count via the Leicester Cough Monitor (LCM). Among 5 (males) patients received sham CPAP and 3 (males) received titrated CPAP. There were no significant differences between groups (mean (SD)) in age (56.3 ± 7.8 years) vs (50.7 ± 10.1 years, p>0.05). In the CPAP group, cough severity was improved in all three group, but it did not significantly differ from sham CPAP group.

Conclusion: Continuous positive airway pressure (CPAP) in subjects with chronic cough and obstructive sleep apnoea improves cough severity.
Results: A total of 53 patients was identified. Average age was 59 years. 35 (66%) were females. 34 (64%) presented with dry cough. 34 (64%) of patients had 2 or more symptoms. 95% of patients had a cause identified by investigations or by a trial of therapy. 45 (85%) had a single aetiology whilst 15% had at least two. 12 (22%) patients had asthma, 9 (16%) reflux, 10 (18%) bronchiectasis, 7 (13%) rhinitis, 6 (11%) sinusitis, 3 (5%) lower respiratory tract infection and 5 (9%) had other diagnoses. Eight (15%) had their symptom completely cured. 17 (32%) had their symptoms controlled of which 15 (88%) were discharged. 28 (52%) of patients were still symptomatic.

Conclusion: The study showed asthma was still the commonest aetiology however this was not as high as seen in other studies. Instead a sizable number of patients had more than one aetiology. Using current diagnostic criteria, early request of HRCT scans in the diagnostic workup of patients with chronic cough is thus recommended.

P485

Outcome of chronic cough referrals seen in general respiratory clinic
Kabali Nandakumar, Kesavaperumal Vijayasarthar. Respiratory Department, Queens Hospital, Burton-on-Trent, Staffordshire, United Kingdom

Aim: Chronic cough is a common symptom for which patients seek medical consultation. Identifying the cause and alleviating their symptoms is a real challenge. In this study we aimed to find the outcome of such patients attending our centre.

Method: This is a retrospective study of patients who were referred with chronic cough to the respiratory clinic between June 09 till June10. Clinical information was obtained from electronic records.

Results: A total of 53 patients was identified. Average age was 59 years. 35 (66%) were females. 34 (64%) presented with dry cough. 34 (64%) of patients were non-smokers. 95% of patients had a cause identified by investigations or by a trial of therapy. 45 (85%) had a single aetiology whilst 15% had at least two. 12 (22%) patients had asthma, 9 (16%) reflux, 10 (18%) bronchiectasis, 7 (13%) rhinitis, 6 (11%) sinusitis, 3 (5%) lower respiratory tract infection and 5 (9%) had other diagnoses. Eight (15%) had their symptom completely cured. 17 (32%) had their symptoms controlled of which 15 (88%) were discharged. 28 (52%) of patients were still symptomatic.

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P486

Accuracy of inhaler and nebulizer prescribing in hospitalized patients
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Introduction: There are a considerable variety of inhaler devices available. It is important that these are prescribed correctly when a patient is admitted to hospital as incorrect prescribing may have an adverse effect on patient recovery and length of stay. We have investigated the accuracy of inhaler prescribing on the respiratory ward in our hospital.

Methods: All admissions into the respiratory wards (total no of beds =57) between March to May 2010 were included (total 83). All case notes were retrieved and wards in our hospital.

Results: Of stay. We have investigated the accuracy of inhaler prescribing on the respiratory
department. A total of 53 patients was identified. Average age was 59 years. 35 (66%) were females. 34 (64%) presented with dry cough. 34 (64%) of patients were non-smokers. 95% of patients had a cause identified by investigations or by a trial of therapy. 45 (85%) had a single aetiology whilst 15% had at least two. 12 (22%) patients had asthma, 9 (16%) reflux, 10 (18%) bronchiectasis, 7 (13%) rhinitis, 6 (11%) sinusitis, 3 (5%) lower respiratory tract infection and 5 (9%) had other diagnoses. Eight (15%) had their symptom completely cured. 17 (32%) had their symptoms controlled of which 15 (88%) were discharged. 28 (52%) of patients were still symptomatic.

Conclusion: The study showed asthma was still the commonest aetiology however this was not as high as seen in other studies. Instead a sizable number of patients had more than one aetiology. Using current diagnostic criteria, early request of HRCT scans in the diagnostic workup of patients with chronic cough is thus recommended.

Table 1. Indications for inhaler/nebulizer prescribing

<table>
<thead>
<tr>
<th>COPD</th>
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</thead>
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<tr>
<td>Asthma</td>
<td>7 (15.9%)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1 (2.3%)</td>
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<tr>
<td>Cystic fibrosis</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>3 (6.6%)</td>
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<tr>
<td>Asthma/Bronchiectasis</td>
<td>4 (9.1%)</td>
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</table>

Table 2. Inhalers/nebulisers prescribed on drug chart

<table>
<thead>
<tr>
<th>BABA inh</th>
<th>BABA nebs</th>
<th>Steroid inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (68.1%)</td>
<td>14 (31.8%)</td>
<td>6 (13.6%)</td>
</tr>
<tr>
<td>Prescribed in hospital</td>
<td>16 (53.3%)</td>
<td>25 (77.1%)</td>
</tr>
<tr>
<td>Correct dose prescribed</td>
<td>4 (13.3%)</td>
<td>12 (85.7%)</td>
</tr>
<tr>
<td>Correct device prescribed</td>
<td>2 (6.7%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abstract P486 - Table 2. Inhalers/nebulisers prescribed on drug chart

P487

Long term efficacy of war related bronchiolitis obliterans treatment
Hamidreza Atefi1, Soheil Fesman1, Maryamossadat Moeniзадeh Tehrani2, 1Pulmonary and Critical Care Department, Imam Khomeini Medical Center; Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran; 2Pulmonary and Critical Care Department, Loghman Hospital, Shahid Behshiri University of Medical Sciences, Tehran, Islamic Republic of Iran

Introduction: There is few data about war related bronchiolitis obliterans (BO) treatment. We compared FVC and FEV1 changes during BO treatment in comparison to non bronchiolitis obstructive pulmonary disease in a cohort of chemical victims.

Materials and methods: Seventy two iranian veterans, with chronic pulmonary disease were followed from September 2005 to December 2010. All of them had documented exposure to Sulfur Mustard gas from 1982 to 1988. The bronchiolitis group (diagnosed based on HRCT and/or biopsy) was treated with inhaled Seretide (500-1000 μg/day), Azithromycin (500 mg3 times per week) and N-acetylcysteine (1200-1800/day). The non bronchiolitis patients were treated according to GINA and GOLD guidelines.

Results: 16 patients had BO and 36 had non bronchiolitis obstructive pulmonary disease.

The baseline FVC and FEV1 were not different between bronchiolitis and non bronchiolitis groups. Mean FVC and FEV1 has decreased significantly during the 5 years followup despite standard treatments in all patients (baseline FVC=3.50±0.78 L, Final FVC=3.21±0.75 L; P=0.001) and (baseline FEV1=2.77±0.80 L, Final FEV1=2.47±0.77 L; P<0.001). The FVC and FEV1 changes in bronchiolitis group were -0.30±0.18L and -0.15±0.521 L respectively. This was not significantly different from FVC and FEV1 changes in non bronchiolitis group (0.29±0.58L and 0.34±0.62 L respectively).

Discussion: The five year spirometric parametric changes were not different between bronchiolitis and non bronchiolitis group in usert saline gas victims. This finding suggests the long term efficacy of treatment with inhaled steroid, macrolide and N-acetylcysteine in war related bronchiolitis obliterans.

P488

Lung function disturbances and BAL IL-6 in adult patients with sickle cell disease in Bahrain
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Sickle cell disease (SCD) is a common genetic disorder of hemoglobin in Bahrain with a lot of pulmonary complications either acute or chronic including its effect on pulmonary function tests (PFT). IL-6 is an inflammatory cytokine that was found to be high in severe SCD patients.

Objective: To study PFT and evaluate BAL IL-6 level in adult Bahraini patients with SCD and to correlate PFT values with BAL IL-6 and the recurrent occurrence of acute chest syndrome (ACS).

Methods: Study was done on 120 subjects (2 groups): group 1 (20 healthy controls) and group 2 (100 adult Bahraini SCD patients during steady state). PFT were done to all subjects. BAL was done to 20 SCD patients and 5 control subjects to evaluate the BAL IL-6.

Results: PFT was abnormal in 85% of SCD patients with restrictive pattern (60%), isolated low DLCO (17%), obstructive pattern (5%) and mixed obstructive and restrictive pattern (3%). BAL IL-6 was higher in SCD patients than in controls. In SCD patients, BAL IL-6 level had significant negative correlations with both FEV1, FVC, DLCO, and PaO2, with no significant correlation with TLC. There were significant positive correlations between BAL IL-6 and both age and number of ACS. There were significant negative correlations between ACS number and both FEV1, TLC and DLCO.

Conclusion: Abnormal PFT in adult Bahraini SCD patients was correlated to BAL IL-6 and number of ACS indicating that impaired lung functions in this category of patients is caused by repeated vascular occlusion and increased airway inflammation.

P489

Caspase activity in patients with chronic refractory unexplained cough
Ewa Teresten Hasselius, Eva Miltqvist. Department of Internal Medicine/Respiratory Medicine and Allergology, Institute of Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Background: When known causes for cough are excluded there still remains a category of patients is caused by repeated vascular occlusion and increased airway inflammation.
a group of patients with persistent coughing. They can be described as having chronic refractory unexplained cough. Sensory hyperreactivity (SHR) is one suggested explanation to cough and other airway symptoms induced by chemicals and scents. The patients can be identified using a capsaicin inhalation test.

The aim was to analyze capsaicin sensitivity in a group of patients with chronic refractory unexplained cough. Further we wanted to evaluate a cough specific questionnaire.

**Method:** From an earlier cross sectional study in patients with chronic cough, 41 patients without chemical sensitivity (non sensitive group) and 35 patients with chemical sensitivity (sensitive group) were involved. The participants underwent a capsaicin inhalation test, and answered the Swedish version of Hull Airway Questionnaire (HARQ). A cut off limit of \( \leq 13 \) score has been suggested as normal.

**Results:** 15 patients in the non sensitive group and 30 in the sensitive group participated. The reason for not participating was in the non sensitive group: recovery (n=19), would not (n=2) and in the sensitive problem: to be away from work (n=5). Capsaicin induced significantly more cough and other airway symptoms in the sensitive group compared to the non sensitive group (p < 0.05).

Mean total HARQ score was 18 in both groups. Conclusion: Chemically induced airway symptoms in chronic refractory unexplained cough, seems to be a prognostic factor that can cause prolonged symptoms. SHR is a possible explanation for this sub-group of cough patients. The HARQ questionnaire has a good ability to identify patients who for various reasons have chronic cough.

**P490**

**Introduction and aim:** Clinical pulmonary infection score (CPS) is a scoring system calculated by symptoms and signs of pneumonia, that is used in the diagnosis and management of hospital acquired pneumonia (HAP). In this study, the comparison of CPS for diagnosis of HAP was investigated in intensive care unit (ICU) patients.

**Methods:** The ICU patients followed-up between February 2008 and September 2010 were assessed retrospectively. Hospital acquired pneumonia was diagnosed by quantitative endotracheal aspirate (ETA). CPS was calculated on 3rd and 7th days of ICU admission. The correlations of CPS with concurrent ETA cultures and laboratory markers of infection were assessed.

**Results:** Out of 240 patients (165 men, mean age 58.2±16.6 yrs) included in the study, ETA cultures were positive in 61 patients (25.4%) on 3rd day, and in 59 patients (24.6%) on 7th day. CPS was found higher in patients with ETA culture positive (5.6±2.3 vs. 3.5±2.1 on 3rd day, p<0.0001; 2.6±2.6 vs. 6.6±2.9 on 7th day, p<0.0001). Sensitivity and specificity ratios of CPS with a threshold level of 6.5 in diagnosis of HAP were 26.2% and 92.3% for 3rd day; 30.5% and 91.9% for 7th day. There was a positive correlation between CPS and C-reactive protein (CRP) levels (p=0.002 and p=0.001, respectively)

**Conclusion:** Clinical pulmonary infection score can be used instead of infection markers like CRP and PCT in the diagnosis of hospital acquired pneumonia.

**P491**

**Implementing a community acquired pneumonia care bundle in the acute hospital setting**

Essam Ramhamadany, Sandra Wilson, Philip Eardley, Jasmin Cheema, Joel Johnson, Kamel Dokhia, May Kay, Ron Grant, Majed Shamat, Eamon Ramhamadany, Bobby Mann, Zul Mira. A&E and Respiratory Department, West Middlesbrough University Hospital, Middlesbrough, Middlesbrough, United Kingdom

**Objective:** The aims are to reliably deliver clinically effective and timely treatment in the management of CAP (community Acquired Pneumonia), to reduce overall variations in care, and to improve the quality of patient care and outcomes.

**Methods:** Using Improvement Methodology techniques the project team: Conducted a base line audit, mapped out current patient journey, arranged education sessions for relevant staff members, used a locally customised CAP bundle pack, and used the PDSA Cycle and the sustainability tools.

A multi professional group, including patient representative, used a bespoke reporting tool to record weekly measures of bundle compliance. Non compliance was disseminated to the team for response and feedback. Project team meetings were held weekly, this gave the opportunity for all to monitor progress.

**Results:** A base line audit of 50 patients was compared with 200 patients in the CAP Care Bundle, over 18 months. There was an improvement in providing written information to patients from 0 to 88%; documenting the CURB-65 CAP severity score 32% to 94%; oxygen correctly prescribed 78% to 88%; timely administration of antibiotics within 4 hours of arrival to hospital from 54% to 88%, and antibiotic following BTS guidelines from 48% to 87%.

**Implications:** Implementing a Care Bundle Pathway can improve patient care, but a high degree of perseverance is required to implement changes and sustain improvements. The success cannot be dependant on only a few champions but needs to have support from the organisation at all levels.

The project was funded and supported by NW London CLAHRC.

**P492**

**Evaluating the efficiency of complex treatment of influenza A (H1N1) in hospital conditions**

Olga Titoiva1, Dmitri Larin1, Vladimir Volchikov1,2. 1Therapeutic Pulmonology, Institute of Pulmonology of I.P.Pavlov State Medical University, St. Petersburg, Russian Federation; 2Therapeutic Pulmonology, Hospital No. 32, St. Petersburg, Russian Federation

**Aim:** To study the efficiency of oseltamivir depending on the time of its administration to patients with typed A (H1N1) and non-typed influenza.

**Methods:** The prospective evaluation of disease severity, frequency of complications and mortality in hospital patients with influenza has been executed. 720 patients with suspicion on a virus infection were surveyed. From them at 373 patients the influenza A (H1N1) was typed by RT-PCR test. Shortness of breath was assessed by MRC scale, severity of patient state was estimated by scale APACHE II. Patients underwent x-rays, laboratory tests, spirometry and diffusion capacity of the lungs.

**Results:** At oseltamivir administration after 48 hours from the disease beginning efficiency of therapy decreased and frequency of complications increased. The severe course of influenza on APACHE II scale was accompanied by an increase in mortality (p<0.05). The disease progressed worsened with an increase of dyspnea at normalization of temperature (p<0.019). The negative impact of obesity and diabetes on the disease course (p<0.004) was revealed.

**Conclusion:** The administration of oseltamivir later than 48 hours from onset of illness, severe state of patients on a scale of APACHE II, the increase of dyspnea after decrease of temperature, obesity and diabetes mellitus are risk factors for complications and adverse outcome of influenza A (H1N1).

**P493**

**Prediction of complications development and lethal outcome in patients with community-acquired pneumonia**

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1Laboratory of Prophylaxis of Nonspecific Lung Diseases, Far Eastern Scientific Center of Pulmonology and Pathology of Respiration SB RAMS; Blagoveschensk, Russian Federation; 2Department of Therapy, Amur State Medical Academy, Blagoveschensk, Russian Federation

**Background:** The prediction of community-acquired pneumonia (CAP) complications development may provide effective prophylaxis and prevent the lethal outcome.

**Aim:** The improvement of prophylaxis of CAP complications development and lethal outcome on the basis of prediction by inflammation markers.

**Methods:** 70 patients with CAP of different severity were examined. When the patient got into hospital his blood serum was tested on the level of procalcitonin (PCT) by immunochromatographic assay. Cytokines IL-2, IL-6 and TNF-α and also C-reactive protein (CRP) were identified by immune-enzyme assay.

**Results:** The level of CRP grew alongside with the severity of CAP, the highest after was 131.5±7.6 mg/l in severe stage (p<0.019). The highest level in patients with complicated clinical course, the highest one was 155.3±44.7 mg/l (p<0.01) at the lethal outcome. The levels of cytokines in patients with developed complications were 2.5 times higher than in the patients without complications. A higher level of PCT was found in patients with complicated CAP (2,36±0,20 ng/ml, p<0.01) in comparison with uncomplicated one. At the lethal outcome the level of PCT was significantly higher (3,67±0,33 ng/ml). To predict the complications development the discriminant equation was derived: D= +3,611 PCT-0,035 CRP +2,281 IL-2 +0,076 IL-6+2,335 TNF-α. If D is more than or equals 15,60, the development of complications is predicted with the probability of 90.1%.

**Conclusions:** The level of PCT, IL-2, IL-6, TNF-α, CRP increases proportionally to severity of CAP. With the help of the proposed equation it is possible to predict the development of complications from the first day of patient getting into hospital.

**P494**

**Findings in peripheral biopsy muscle in severe pneumonia due to H1N1 influenza**

Maria Eugenia Dominguez Flores1, Monica Velazquez1, Rafael J. Hernandez-Zenteno2, Franciscas Fernandez Valverde3, Steven Vargas Cañas4.

1Laboratory of Prophylaxis of Nonspecific Lung Diseases, Far Eastern Scientific Center of Pulmonology and Pathology of Respiration SB RAMS; Blagoveschensk, Russian Federation; 2Department of Therapy, Amur State Medical Academy, Blagoveschensk, Russian Federation

**Rationale:** Myalgia and weakness are complications in H1N1 Influenza severe course, Myopathy and polyneuropathy has been described only in Influenza B. Muscle damage in H1N1 ISP, has not been studied yet.
Objective: To evaluate physiological, morphological and metabolic characteristics in muscle biopsies from patients with severe muscular weakness after a H1N1 ISP

Case report: After signed consent form 14 subjects with H1N1 ISP and muscular weakness were enrolled. Bilateral muscular strength (biceps and quadriceps) measured by electronic manometer and electromyography and muscle biopsy (3-5 days after extubation) were performed.

Results:

General and Clinical characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>CK &gt; 360 U/L</th>
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<th>S/min</th>
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<td>11</td>
<td>Yes</td>
<td>SMP</td>
<td>MN</td>
<td>M</td>
</tr>
</tbody>
</table>

M = male, F = female, CK = creatin kinase, APACHE II = Acute Physiology and Chronic Health Evaluation, MV = mechanical ventilation, S = percent predicted average of 4 muscles, EMG = electromyography, SMP = sensoriotor motor polymyelopathy, M. pneumoniae = mixed pattern myopathy and neuropathy, M = myopathy (metabolic).

Conclusions: All patients with H1N1 ISP presented metabolic and physiological muscular alterations compatible with myopathy or myopathy/neuropathy. This findings explain the severe muscle symptoms and the low recovering even after discharge. An early physical rehabilitation program must be recommended.

P495

Bacterial profile, antibiotic sensitivity and resistance of lower respiratory tract infections in upper Egypt

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Chest Diseases, Faculty of Medicine, El-Minia University, El-Minia, Egypt.

Chest Diseases, Faculty of Medicine, Sohag University, Sohag, Egypt.

Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Purpose: To identify causative bacteria, antibiotic sensitivity/resistance of lower respiratory tract infections (LRTIs) in Upper Egypt.

Methods: A multicentre prospective study was performed. Sampling was done for all patients including, sputum and/or BAL for Gram stain and culture. Samples were cultured on 3 media (Nurtient,Chocolat and M-Aconkey's) until Fluorescent Antibody was used to detect atypical pathogens.

Results: Predominant isolates in patients with CAP were S. pneumoniae (36%), C. pneumonia (18%), M. pneumoniae (12%) and K. pneumoniae (10%). A higher sensitivity was recorded for moxiﬂoxacin, levofloxacin, macrolides, and cepﬁclozine. A higher rate of resistance was recorded for tetracyclines, cephalosporins, lincomma, and β-lactam-β-lactamase inhibitor. Predominant isolates in patients with HAP were, MRSA (23%), K. pneumoniae (14%), E. coli (11%), PaeCREATINOSA (9%). A higher resistance was recorded for vancomycin,amikacin, and respirato- ry quinolones. An absolute resistance was recorded for β-lactam-β-lactamase inhibitor, high rates were recorded for cephalosporins. Predominant isolates in patients with AECOPD were H.influenza (30%), S. pneumoniae (25%), M. catarrhalis (18%), K. pneumoniae (12%) and C. pneumoniae (5%). A higher sensitivity was recorded for amikacin,clindamycin, and cephalosporins.

Conclusion: The most predominant bacteria for CAP in Upper Egypt are S. pneumoniae and atypical organisms, while that for HAP are MRSA and Gram negative bacteria. For AECOPD, H.influenza is the commonest. Respiratory quinolones, linezolid, and cepﬁclozine are the most efﬁcient antibiotics in treating LRTIs in our locality.

P496

Arterial hypoxemia and diminished immune response at admission predict poor outcome in patients with viral-bacterial pneumonia during flu H1N1 pandemic period

Rustem Zulkaernev1, Shamil Zagaindullin2, Maksar Sadrzidinov2, Usman Farhutdinov2, Veronika Leshkova2, Natalia Vlasova1, Venera Mustafina1.

1Internal Diseases (Propedeutics), Bashkortostan State Medical University, Ufa, Bashkortostan, Russian Federation; 2Anesthesiology and Critical Care, Bashkortostan State Medical University, Ufa, Bashkortostan, Russian Federation;

3Pulmonology, Clinical Hospital No. 21, Ufa, Bashkortostan, Russian Federation

Severe flu associated respiratory infections remain actual.

Aim: To evaluate the prognostic model of outcome of severe viral-bacterial community acquired pneumonia (VBCAP) during flu H1N1 pandemic based on hospital admission data.

Materials: 84 patients (43 survivors and 41 non-survivors) admitted with VBCAP in hospitals of Bashkortostan region between November and December 2009 were included in the retrospective study. The endpoint was defined as hospital mortality.

Methods and results: Initially 16 demography, history, functional and laboratory variables were obtained from hospital admission records. In the univariate ROC analysis, 5 variables were correlated with poor outcome of VBCAP.

Univariate ROC-analysis results

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under ROC-curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2 &lt;90%</td>
<td>72,7</td>
<td>93,9</td>
<td>0.89 (0.78-0.96)</td>
</tr>
<tr>
<td>Breathing rate &gt;20/min</td>
<td>86,4</td>
<td>66,7</td>
<td>0.84 (0.71-0.92)</td>
</tr>
<tr>
<td>Serum glucose &gt;5 mmol/l</td>
<td>77,5</td>
<td>63,6</td>
<td>0.69 (0.55-0.81)</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>68,2</td>
<td>69,7</td>
<td>0.68 (0.54-0.80)</td>
</tr>
<tr>
<td>WBC &lt;6.9 x 10^9/l</td>
<td>50,0</td>
<td>84,8</td>
<td>0.68 (0.54-0.80)</td>
</tr>
</tbody>
</table>

Cutoffs were used to transfer continuous variables to dichotomous ones. Multivari- ate stepwise logistic regression analysis identified SpO2% and white blood cell count as independent predictive factors at p < 0.05.

Logistic regression equation:

logit P = 3.49 + SpO2% - 0.90 - 2.24 x WBC -6.9 x 10^9/l - 1.76, where P = poor outcome probability. Correct classification rate was 82.8%.

Conclusion: Acute respiratory failure and diminished immune response are the most powerful independent prognostic factors of poor outcome of viral-bacterial pneumonia during flu H1N1 pandemic.

P497

Comparison of telomerase activity in malignant and benign pleural effusions

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Background: Despite advances in diagnosis and treatment of lung cancer, patients survival has just improved in those with early stages. Telomerase is a tumor marker that has been focused recently as a novel tool for early diagnosis of lung cancer.

Objective: To compare telomerase activity in malignant and benign pleural effusions in Rasoul-e-Akram Hospital of Tehran.

Methods & materials: Telomerase activity in 28 consecutive pleural effusions (19 malignant and 9 benign; histopathologic diagnosis) assessed with telomeric repeat amplification protocol (TRAP) between Apr. 2006 and Sep. 2007. Data analysis was performed by chi-squared test and t-test; results expressed as frequency, percent, and mean ± SD.

Results: 20 cases (71.4%) from the total of 28 pleural effusions were positive for telomerase activity. Telomerase activity was positive in all 19 malignant effusions, while only one effusions from benign conditions (TB) had telomerase activity (P = 0.0001). Sensitivity, specificity and diagnostic accuracy of telomerase activity for detecting malignant pleural effusions were 100%, 88.9% and 96.4% respectively. Mean telomerase relative activity in malignant and benign effusions was not significantly different (24 ± 5.2% vs. 15.05%; P = 0.05).

Conclusion: Telomerase activity is a highly sensitive and specific diagnostic biomarker for malignancy and may be used as an adjunct to other diagnostic tools such as cytological findings for malignant pleural effusions.

P498

Evaluation of the utility of using pleural fluid cholesterol as a new criterion for the differential diagnosis between transudates and exudates

Kostas Kosmidis, Stefanos Pataiakas. General Hospital of Kastoria, Microbiological Laboratory and Respiratory Department of General Hospital of Kastoria, Kastoria, Greece.

Objective: To study two alternative criteria to differentiate between exudates and transudates: a) pleural fluid cholesterol and b) the ratio of pleural fluid cholesterol to serum cholesterol in order to compare their diagnostic value with the widely accepted and used Light’s criteria.

Method: 97 patients with pleural effusion were tested. According to Light’s criteria, there were 29 transudative and 68 exudative pleural effusions. Pleural fluid and serum levels of lactate dehydrogenase, protein and cholesterol were measured using colorimetric methods and a biochemical analyzer.

Results: Using as a cut-off value for the pleural fluid cholesterol the value of 65mg% (the upper limit to identify a pleural effusion as a transudate) this criterion yielded a sensitivity of 87% and a specificity of 79%. Using the alternative criterion of pleural fluid cholesterol to serum cholesterol ratio (and a cut-off level of 0.4 as the upper limit to identify a transudate) the sensitivity was 87% and the specificity was even greater at 81%.

Conclusions: This study showed that using pleural fluid cholesterol and pleural fluid cholesterol/serum cholesterol ratio may be useful for the differential diagnosis between transudates and exudates, and can provide assistance especially where other criteria are marginal or ambiguous.
In this non-interventional study, telmisartan proved to be generally well tolerated and highly effective in alleviation of dry cough resulting from primary care (CAPHRI), Maastricht University Medical Centre, Maastricht, Tadeusz Lietz1, Michal Wronka 2, Jerzy Kozielski3.

Broncholithiasis is defined as the presence of a calcified fragment of tissue within a bronchus. It almost invariably represents the end-stage of healing of granulomatous diseases such as histoplasmosis or tuberculosis. Broncholiths are found with almost equal frequency in men and women, mostly in the fifth or sixth decade. Common symptoms are chronic cough, hemoptysis and sputum. Lymphoceilysis, which is pathogenic, is rare. The chest radiograph mostly shows calcified masses around the bronchi. In most cases, because of no significant symptoms or complications, observation may be the best course but bronchoscopic removal or surgical interventions are indicated in some instances. From June 1996 to December 2010, 24 patients with broncholithiasis had undergone the analysis for clinical manifestation, bronchoscopic finding, treatment modality and follow-up status. Broncholithiasis was developed in association with tuberculosis in 45.8% and locations corresponded in 54.5%. Lymphoceilysis occurred in 20.8%. Obstructive pneumonia was the most common radiographic finding, and calcification was found in 50.0%. Various positive findings, noted in all patients undergoing flexible bronchoscopy, included visible broncholith, granulation tissue or blood clots. In follow-up patients, while all patients with conservative care only continued to have symptoms, an excellent result was evident in 8 of 11 patients in whom broncholith was removed after treatment or spontaneously. A clinical awareness of the manifestations of broncholithiasis will result in early diagnosis and treatment. If the broncholith can be removed, as indicated, before irreversible distal bronchial and parenchymal damages occur, the long-term outlook for symptomatic relief is excellent.

76. Innate and exogenous factors in childhood respiratory infection

P501

Bacterial colonisation/infection and airway inflammation in prematurely born children with recurrent wheeze
Kim Dicke van de Kant1, Ester M.M. Klaassen1, Koen van Aarde1, Cathren Bruggeman2, Foeke Stelma3, Ellen Stobberingh2, Ger T. Rijkers1,2, Jean W.M. Muris4, Quirijn Jobuis5, Onno C.P. van Schayck6, Edward Dompeling7.1 Paediatrician, School for Public Health and Primary Care (CAPHRI), Maastricht University Medical Centre, Maastricht, Netherlands; 2Medical Microbiology, School for Public Health and Primary Care (CAPHRI), Maastricht University Medical Centre, Maastricht, Netherlands; 3University Medical Centre Utrecht, Utrecht, Netherlands; 4Medical Microbiology and Immunology, Sint Antonius Hospital, Nieuwegein, Netherlands; 5Reproductive Medicine, Inha University Hospital, Incheon, Korea

Broncholithiasis is a chronic disease, the prevalence of which increases with age. The pathogenesis of broncholithiasis involves the interaction of bacterial, immunologic, and host factors. Broncholithiasis is defined as the presence of a calcified fragment of tissue within a bronchus. It almost invariably represents the end-stage of healing of granulomatous diseases such as histoplasmosis or tuberculosis. Broncholiths are found with almost equal frequency in men and women, mostly in the fifth or sixth decade. Common symptoms are chronic cough, hemoptysis and sputum. Lymphoceilysis, which is pathogenic, is rare. The chest radiograph mostly shows calcified masses around the bronchi. In most cases, because of no significant symptoms or complications, observation may be the best course but bronchoscopic removal or surgical interventions are indicated in some instances. From June 1996 to December 2010, 24 patients with broncholithiasis had undergone the analysis for clinical manifestation, bronchoscopic finding, treatment modality and follow-up status. Broncholithiasis was developed in association with tuberculosis in 45.8% and locations corresponded in 54.5%. Lymphoceilysis occurred in 20.8%. Obstructive pneumonia was the most common radiographic finding, and calcification was found in 50.0%. Various positive findings, noted in all patients undergoing flexible bronchoscopy, included visible broncholith, granulation tissue or blood clots. In follow-up patients, while all patients with conservative care only continued to have symptoms, an excellent result was evident in 8 of 11 patients in whom broncholith was removed after treatment or spontaneously. A clinical awareness of the manifestations of broncholithiasis will result in early diagnosis and treatment. If the broncholith can be removed, as indicated, before irreversible distal bronchial and parenchymal damages occur, the long-term outlook for symptomatic relief is excellent.

P502

Small airway function in prematurely born infants following viral infection
Simon Drysdale1, Mireia Akaizar1, Therese Wilson1, Melvyn Smith1, Mark Zuckerman2, Simon Roughton3, Sean Fitzgerald1, Tadeusz Lietz1, Michal Wronka2, Jerzy Kozielski3.

Aims: To study whether preschool children with recurrent wheeze differ in bacterial infection/colonisation in the upper respiratory tract compared with healthy controls.

Methods: We recruited 252 children aged 2-4 years with (n=202) and without (n=50) recurrent wheeze. Nasal and throat swabs were analysed for the presence of Streptococcus (S.) pneumoniae and Haemophilus (H.) influenzae. Sero-sensitivity for Chlamydia (C.) and Mycoplasma (M.) pneumoniae was assessed by ELISA collected using a closed-glass condenser. Inflammatory markers (Interleukin (IL)-4, IL-8, IL-13) in EBC were measured using multiplex immunoassay.

Results: Only positive serology for M. pneumoniae was slightly higher in children with recurrent wheeze compared with healthy controls (11% vs. 2%, p=0.09). Wheezing children colonised with H. influenzae (N=61) had higher levels of all interleukins compared with colonised children without recurrent wheeze (N=15) (p<0.05).

Conclusion: We found no convincing evidence for an association between bacterial colonisation/infection and preschool recurrent wheeze. Airway colonisation with H. influenzae leads to elevated pro-inflammatory markers in recurrent wheezers, indicating augmented airway inflammation in these children.

P503

IL-872 isoforms in lung of preterm infants and its processing by neutrophil serine proteases
Silvia Elena Akavoliv, Nikolai Voitenok1, Sislej Kotecha, Edward Dompeling1, 2 Department of Child Health, Cardiff University, Cardiff, United Kingdom; 3Laboratory of Cellular and Molecular Immunology, Research Centre for Haematology and Transfusiology, Minsk, Belarus; 4 Fund for Molecular Hematology and Immunology, Fund for Molecular Hematology and Immunology, Moscow, Russian Federation

Introduction: Persistent neutrophilic (PMN) lung inflammation is strongly influenced in the development of Chronic Lung Disease (CLD) of Prematurity. The 72 amino acid (a.a.) chemokine, IL-872, is a key molecule involved in attracting PMNs to sites of inflammation. The longer 77 a.a. isoform (IL-877) is less potent than IL-872 in vitro. We studied expression of IL-872 in the preterm ventilated lung and its processing by neutrophil serine proteases. Methods: IL-872 was measured by ELISA in bronchoalveolar lavage fluid (BALF) from ventilated preterm infants born at ≤ 32 weeks gestational age and after correction by purified Cystein protease serine proteases. Results were compared between the CLD (persistent inflammation) and non-CLD groups (resolved).

P499

A clinical study on broncholithiasis
Hong Yee Lee; Hae Sung Nam; Jae Hwa Cho; Jeong Seon Ryu. Department of Internal Medicine, Inha University Hospital, Incheon, Korea

Broncholithiasis is defined as the presence of a calcified fragment of tissue within a bronchus. It almost invariably represents the end-stage of healing of granulomatous diseases such as histoplasmosis or tuberculosis. Broncholiths are found with almost equal frequency in men and women, mostly in the fifth or sixth decade. Common symptoms are chronic cough, hemoptysis and sputum. Lymphoceilysis, which is pathogenic, is rare. The chest radiograph mostly shows calcified masses around the bronchi. In most cases, because of no significant symptoms or complications, observation may be the best course but bronchoscopic removal or surgical interventions are indicated in some instances. From June 1996 to December 2010, 24 patients with broncholithiasis had undergone the analysis for clinical manifestation, bronchoscopic finding, treatment modality and follow-up status. Broncholithiasis was developed in association with tuberculosis in 45.8% and locations corresponded in 54.5%. Lymphoceilysis occurred in 20.8%. Obstructive pneumonia was the most common radiographic finding, and calcification was found in 50.0%. Various positive findings, noted in all patients undergoing flexible bronchoscopy, included visible broncholith, granulation tissue or blood clots. In follow-up patients, while all patients with conservative care only continued to have symptoms, an excellent result was evident in 8 of 11 patients in whom broncholith was removed after treatment or spontaneously. A clinical awareness of the manifestations of broncholithiasis will result in early diagnosis and treatment. If the broncholith can be removed, as indicated, before irreversible distal bronchial and parenchymal damages occur, the long-term outlook for symptomatic relief is excellent.
Results: The majority of IL-8 consisted of the shorter isoforms in the preterm lung (96.3% non-CLD vs 97.1% CLD, p=ns). IL-8 signalling correlated well with total IL-8 (p<0.0001) but not with gestation (p=ns). Stimulated adult airway cells and neonatal PMNs and monocytes expressed IL-8's as the major isoform, suggesting possible expression in the lung. Preterm BALF significantly converted rHL-8 to shorter isoforms at 18 hours (p<0.05), which was inhibited by α-antitrypsin (AAT). Purified neutrophil serine proteases converted IL-8 to shorter isoforms dose-dependently and over time.

Conclusions: Majority of IL-8 in the ventilated preterm lung are the potent shorter isoforms. Although potentially expressed in the lung, IL-8's is probably converted to the shorter isoforms by neutrophil serine proteases. Inhibition of conversion by AAT suggests a potential therapeutic role for it in modulating inflammation in the preterm lung.

P304 Expression and functional activity of IL-6, sIL-6R & sgp130 in the preterm infant lung
Maliniath Chakraborty1, Eamon McGreal1, Philp Davies1, Simon Jones2, Saisheel Kotecha1, 1Department of Child Health, Cardiff University, Cardiff, United Kingdom; 2Department of Medical Biochemistry and Immunology, Cardiff University, Cardiff, United Kingdom

Introduction: Persistent neutrophil-dominated lung inflammation is strongly implicated in the development of Chronic Lung Disease of Prematurity (CLD). The complex of interleukin-6 (IL-6) and its soluble receptor, sIL-6R, can activate signalling in cells lacking the cell-surface receptor IL-6R; a soluble form of the signal-transducer gp130 can inhibit trans-signalling by specifically binding to the sIL-6R/gp130 complex. As anti-inflammatory effects of IL-6 trans-signalling can shape resolution of inflammatory responses, we studied the expression, inter-relationships and functional activity of IL-6, sIL-6R and sgp130 in the preterm lung.

Methods: Cytokines were measured by ELISA in bronchoalveolar lavage fluid (BALF) from ventilated preterm infants born at <32 weeks gestational age. Functional activity was determined in a sensitive, IL-6 specific bioassay using mouse B9 cells. Results were compared between the CLD group (persistent inflammation) and non CLD (resolution) group (resolved).

Results: Inflammatory cells and chemokines, CXCL8 and CCL2, were higher in the CLD group (p<0.05). IL-6 and sIL-6R were comparable between the two groups; however, gp130 was higher in the CLD group (CLD 65.3 ng/ml vs non CLD 20.8 ng/ml p=0.01), as was the anti-trans-signalling ratio of sgp130/sIL-6R (p=0.01). Functional activity of IL-6 in the bioassay was similar between the two groups. Trans-signalling activity was not noted in any of the samples in the bioassay.

Conclusions: Increased sgp130 in the lungs of preterm infants may be responsible for impaired trans-signalling by the sIL-6R/gp130 complex. Better understanding of this pathway may lead to therapies to resolve lung inflammation in preterm infants.

P305 Cytokine response in pediatric patients with pandemic H1N1 influenza virus infection and pneumonia: Comparison with pediatric pneumonia without H1N1 infection
Myung Chul Hyun, Dong Won Lee, Yeo Hyang Kim. Pediatrics, Kyungpook National University School of Medicine, Daegu, Republic of Korea Pediatrics, Inje University College of Medicine, Pusan, Republic of Korea Pediatrics, National University School of Medicine, Daegu, Republic of Korea

Objectives: We investigated serum cytokine levels in pediatric patients with pandemic H1N1 virus infection pneumonia and in pediatric patients with pneumonia but without H1N1 infection, and examined correlations between cytokine levels and clinical/laboratory findings.

Methods: Fifty-seven cases of infection by H1N1 virus were confirmed by RT-PCR and enrolled. Of these 57 cases, 26 had a severe H1N1 infection (group 1), and 31 had a mild H1N1 infection (group 2). Sera from 18 cases with pneumonia without H1N1 infection (group 3) were used as controls. The serum levels of 10 cytokines were determined by multiplex assay.

Results: The serum levels of IFN-α, IL-6, and IP-10 were significantly higher in H1N1 infected cases than in group 3, and levels of IL-6 and IP-10 were significantly higher in group 1 than in group 2. The level of IL-10 was significantly higher in groups 1 and 3 than in group 2. However, levels of IFN-α, TNF-α, and IL-17 were not significantly different between the three groups. IL-1β, IL-4, and MIP-1α were not detectable in most patients. IP-10 and IL-6 levels were found to show negative correlations with lymphocyte count and oxygen saturation.

Conclusions: We found higher levels of cytokines (IFN-α, IL-6, IP-10) of innate immunity than those of acquired immunity in pediatric H1N1 infection. Of the cytokines to be found in cases with a H1N1 infection, IP-10 and IL-6 were found to be correlated with disease severity (lymphopenia and hypopnoea). IP-10 and IL-6 may be important markers in pediatric H1N1 infection.

P306 Respiratory symptoms correlate with pulmonary inflammation at a time of presumed stability in children with non-ambulant neurodisability
Ruth Trinick1,2, Anthony M. Dalzell1, Paul S. McNamara1,2, 1Department of Women's and Children's Health, University of Liverpool, Liverpool, United Kingdom; 2Department of Respiratory Medicine, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom; 3Department of Gastroenterology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom

Background: Children with non-ambient neurodisability (ND) often have chronic respiratory symptoms which impact on quality of life and can result in multiple hospital admissions. Respiratory complications are a leading cause of death in this group.

Aims: Assess respiratory symptoms and broncho-alveolar lavage (BAL) inflammatory markers at a time of presumed stability.

Methods: Children with ND and healthy controls were recruited during elective surgical admission. A respiratory symptom score (LRoQ) was completed. BAL was taken at anaesthetic induction. Neutrophil count was recorded (% total cells). IL-8 and TGF-β1 were measured by ELISA. Data are expressed as median [IQR].

Results: 16 children with ND had higher LRoQ scores than 10 controls (21 [5-46] vs. 5 [0-7], p<0.02). Children with ND had greater BAL neutrophilia (52% [31-71] vs. 4% [3-12], p<0.01) and higher IL8 (516 [0-2465] vs. 0 [0-232] pg/ml, p<0.05). Median TGF-β-1 did not differ (0 vs.0 but the range was markedly different (0-271 vs 0.73 g/ml). LRoQ score correlated with BAL neutrophilia (r=0.54, p<0.01), IL8 (r=0.49, p<0.01) and TGF-β-1 (r=0.43, p<0.01). No ND patients had seen a respiratory specialist, 8/16 had undergone video-fluoroscopy (7/8 v e) and 2/16 took antibiotic prophylaxis.

Conclusions: Children with ND have a high burden of respiratory symptoms which correlate with chronic airway neutrophilia and raised inflammatory cytokines at times of presumed stability. A screening tool to identify those children who would benefit from a specialist respiratory review would be useful. Further research into the potential benefits of prophylactic therapy in this group is needed.

P307 Subclinical vitamin D deficiency and acute respiratory tract infections in children: A systematic review
Anjay M.A. Pillai1, Vijay Palanivel2, 1Paediatric Respiratory Medicine, Great Ormond Street Hospital for Children, London, United Kingdom; 2Paediatric Neurodisability, Chelsea & Westminster Hospital, London, United Kingdom

Rickets has historically been considered as a risk factor for development of pneumonia, primarily due to mechanical factors such as rib cage abnormalities and hypotonia. However, the association between vitamin D levels and acute respiratory tract infections (RTI) in children without rickets has not been thoroughly explored so far.

Aims: We aim to systematically review the available literature regarding:

• Association of low Vitamin D levels with RTI in children without clinical rickets
• Role of Vitamin D supplementation in prevention and treatment of RTI.

Methods: Structured systematic literature search

Results: Seven papers on association of low Vitamin D levels and RTI were obtained. See Table 1.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Population</th>
<th>Study Type</th>
<th>Outcomes (see the question)</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective cohort study</td>
<td>Association of infants with treatment outcome, association of vitamin D deficiency (as measured by 25(OH)D) with neutrophils counts and resolution of RTI</td>
<td>Treatment failure higher in [group (DR] vs control group (CR): DR=1.5 (95% CI 1.2-1.8), p&lt;0.001, VDI strongly associated with reduced 25(OH)D (OR 0.71, 95% CI 0.53-0.95, p=0.003), VDI associated with increased risk of RTI (OR 2.56, 95% CI 1.17-5.63, p=0.02).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary analysis of a national cross-sectional sample</td>
<td>Association between serum 25(OH)D levels and rate of upper RTI</td>
<td>Caseload care /25(OH)D levels lower in caseload group compared to control group (p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case control study</td>
<td>Association between bronchiolitis and pneumonia, control group compared with respirator symptoms 25(OH)D levels</td>
<td>Caseload care /25(OH)D levels lower in caseload group compared to control group (p=0.03)</td>
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<td>Mean difference 25(OH)D levels between caseload and control groups (p=0.05)</td>
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<td>Mean difference 25(OH)D levels between caseload and control groups (p=0.05)</td>
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</tbody>
</table>

Two papers, both double blinded randomised controlled trials (RCT), were identified on Vitamin D supplementation in RTI. See Table 2.

Conclusions: Our literature review has revealed that subclinical vitamin D levels are strongly associated with risk of acquiring RTI as well as increased RTI-
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**P508**

Risk factors for wheezing and allergy in preschool children (PSC) after admission for acute bronchiolitis

Ana Saianda1, Sandra Lobo2, Sara Aguilar1, Raquel Gouveia1, Ana Silva1, Tiago Silva2, Filipa Negreiro3, Teresa Banderia1, 1Lung Function, Sleep and Ventilation Unit, Clinica Universitaria de Vitoria, University Hospital of Santa Maria, Lisbon, Portugal; 2Peditric Service, Hospital District of Cascais, Cascais, Portugal; 3Eurotrials – Scientific Consultants, Eurotrials, Lisbon, Portugal

Introduction: Acute bronchiolitis (AB) is associated to later development of wheezing (W) and allergic sensitisation, but risk factors remain controversial. This study aimed to test the hypothesis that clinical background and features of the acute episode influences outcomes.

Methods: A cross-sectional study was performed in 71 out of 340 infants <2-year-old admitted for AB (Oct/02-Apr/04) in a tertiary teaching hospital. We conducted structured interviews, spirometry and skin-prick tests (SPT) to common infant allergens to 4-6 year-old and looked for demographic and clinical risk factors (male gender, birth season, prematurity, exposure to smoke, nursery,older siblings, pets, family history of allergy, no breast feeding) and for the acute episode (RSV, age <6 weeks, severity [length of hospital stay ≥6 days and time on oxygen ≥4 days]) and use of steroids. Main outcomes were any episode of W and persistent wheezing (PW).

Results: W occurred in 50 (70%) of children, but only 19 (39%) referred PW. We found no differences between groups, except for steroid treatment at acute episode [W 6 (12%)/not W 8 (38%)] that was associated with a 4.5 risk reduction of wheezing (adjusted OR [IC] 0.22 [0.065-0.76]) but not for PW. PW was associated with positive SPT [PW 7 (39%); no PW 3 (10%)], adjusted OR [IC] 3.7 (1.4-10.2).

Conclusion: This study shows a high prevalence of wheezing in PSC after AB (Oct/02-Apr/04) in a tertiary teaching hospital. We conducted structured interviews, spirometry and skin-prick tests (SPT) to common infant allergens to 4-6 year-old and looked for demographic and clinical risk factors (male gender, birth season, prematurity, exposure to smoke, nursery,older siblings, pets, family history of allergy, no breast feeding) and for the acute episode (RSV, age <6 weeks, severity [length of hospital stay ≥6 days and time on oxygen ≥4 days]) and use of steroids. Main outcomes were any episode of W and persistent wheezing (PW).

**P509**

Effect of salbutamol on the growth, virulence and biofilm formation of pseudomonas aeruginosa

Priti Kenia, Primrose Freestone, Christopher O’Callaghan. Department of Infection, Inflammation and Immunity, University of Leicester, Leicester, United Kingdom

Background: Beta-2-agonists, like salbutamol are commonly used in patients with lung disease such as cystic fibrosis where chronic infection is common. Recently salbutamol was shown to have an effect on host defence in a murine model, impairing clearance of Haemophilus influenzae from the respiratory tract [1]. To determine if salbutamol affected bacterial virulence, we investigated the effect salbutamol had on the growth and virulence of Pseudomonas aeruginosa(PA).

Aims: To determine if salbutamol affects the growth, virulence and biofilm production of PA.

Methods: Clinical isolates of PA were used for experiments with and without addition of salbutamol at a range of concentrations between 0.375-100 microgram/ml. Viable colony counts and growth curve were performed to determine bacterial growth. Biofilm formation was studied using attachment crystal violet assay, light and advanced microscopy and electron microscopy using 1 cm2 endotracheal tube pieces.

Results: There was no difference in the growth of PA in the presence of salbu-


tamol. However, at low concentrations of salbutamol (1 mg/ml) there was a significant increase in bacterial clumping on light microscopy and increased biofilm formation on endotracheal tube sections on electron microscopy.

Conclusions: Salbutamol appears to increase biofilm formation of Pseudomonas aeruginosa. This study does not imply that the use of beta-2-agonist be discouraged but suggests that a potential role in the virulence of PA must be investigated.

**References:**


**P510**

RANTES gene promoter polymorphisms -28C/G and -403G/A in children hospitalized with community acquired pneumonia

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The course of community acquired pneumonia in children varies between patients and it is common belief that the innate immune system of the host plays an important role to the outcome of the infection. The chemokine RANTES is an important chemoattractant which attracts monocytes, T cells, NK cells and eosinophils into sites of inflammation.

Aim of the study was to investigate the frequency of -28C/G and -403G/A RANTES polymorphisms in children hospitalized with community-acquired pneumonia. The study involved two groups of children. The first (group A) consisted of 60 children hospitalised with pneumonia, 37 boys, aged 5.0±4.4 years and the second (group B) consisted of 135 healthy children, 60 boys, aged 9.6±6.0 years with no history of respiratory infections.

The genotypes of all subjects were determined with PCR-RFLP assay.

**Frequency of genotypes and alleles of RANTES –28 C/G and –403 G/A polymorphisms**

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Group A</th>
<th>Group B</th>
<th>Alleles</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_28 C/G</td>
<td>C/C (%)</td>
<td>130 (97.01)</td>
<td>C</td>
<td>263 (97.02)</td>
<td>C</td>
</tr>
<tr>
<td>R_28 C/G</td>
<td>C/G (%)</td>
<td>44 (3.59)</td>
<td>G</td>
<td>7 (0.26)</td>
<td>G</td>
</tr>
<tr>
<td>R_403 G/A</td>
<td>G/G (%)</td>
<td>100 (75.97)</td>
<td>A</td>
<td>70 (24.03)</td>
<td>A</td>
</tr>
<tr>
<td>R_403 G/A</td>
<td>G/G (%)</td>
<td>90 (67.92)</td>
<td>G</td>
<td>53 (18.33)</td>
<td>G</td>
</tr>
</tbody>
</table>

According to the results, only the -28C/G RANTES promoter polymorphism is associated with community-acquired pneumonia in children. No association was found for the -403G/A polymorphism.

**P511**

Diagnosis of primary ciliary dyskinesia in a Dutch cohort of 63 pediatric patients: An overview

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The diagnosis of primary ciliary dyskinesia (PCD) is difficult, as a single gold standard is lacking. The diagnosis is usually based on a combination of clinical symptoms, abnormal movement of cilia on microscopic evaluation of respiratory epithelial biopsies (LM) and/or epithelial cell cultures (CLM), or identification of an ultra-structural defect in the cilium by electron microscopy (EM). In order to get more insights into the diagnostic value of each of these tests, we performed a retrospective analysis in a cohort of 63 pediatric PCD patients treated within our center. Patient characteristics were as follows: mean age at diagnosis 3.8 years (range 0-18 years), males 44%, females 56% and sinus inversus 39.7%. PCD was diagnosed based on a combination of clinical symptoms and LM in 7.9%, EM 4.8%, CLM 1.6%, LM and CLM 36.5%, LM and EM 20.6%, or LM, EM and CLM in 28.6% of the patients respectively. Abnormal beat frequency, amplitude and coordination observed in epithelial cell cultures from PCD patients, correlated with dyskinetic movement observed in the original biopsies (p<0.01). However, secondary dyskinesia is often encountered in nasal biopsies, as is illustrated by the fact that in 67 out of 136 biopsies with dyskinetic cilia obtained during the last 2 years, cell culture results were normal. In 28.6% of the PCD patients, EM findings were normal. In summary, the diagnosis of PCD cannot rely on a single technique, as both false negative and false positive results frequently occur. Epithelial cell cultures should be an integral part of the diagnostic work-up. Future studies into the genetic background may further improve diagnostic accuracy.

**P512**

What is the gold standard in the diagnosis of primary ciliary dyskinesia syndrome?

María Teresa Romero Rubio1, Miguel Armengot Carceller2, Carmen Carda Batalla2, Amparo Escobedо Montaner1, Javier Milara Paya1, 1Pneumology Department, Department of Pediatrics, Hospital de Denia, Denia, Alicante, Spain; 2Department of Otolaryngology, Hospital General Universitario, Valencia, Spain.

According to the results, only the -28C/G RANTES promoter polymorphism is associated with community-acquired pneumonia in children. No association was found for the -403G/A polymorphism.
Introduction: The diagnosis of primary ciliary dyskinesia (PCD) is based on the study of ciliary motility (frequency and beat pattern) using high resolution digital video and high speed, combined with ciliary ultrastructure by electron microscopy (EM.) However, this can provide false positives and negatives, so the final diagnosis is defined by the ciliary function.

Objectives: To study the real prevalence of PCD after the introduction of the technique of ciliary motility in our center (2007). To set the number of cases previously classified PCD who have a normal ciliary motility.

Material and methods: Study of frequency and ciliary beat pattern: a) in patients who had been diagnosed from PCD until 2007 by screening of mucociliary clearance with 99mTc-labeled albumin and abnormal ciliary ultrastructure. b) in patients with clinical suspicion of PCD, from February 2007 to December 2010.

Results: a) Prior to the introduction of the technique the diagnosis of PCD was made in 17 cases. With the study of motility, we obtain a normal frequency/beat pattern in 8 of them (47%), dyskinetic in 6 cases (35%), not being possible to do in 3 of them. Therefore, the diagnosis of PCD is reduced 42.8%. 37.5% of confirmed cases associated with sinus inversus (S. Kartagener). b) Since 2007 we have studied 79 patients with clinical suspicion of PCD obtaining a dyskinetic pattern in 4 cases (5%), of which only 1 (25%) had anomalous ciliary ultrastructure.

Conclusions: The diagnosis of PCD based on the study of ciliary ultrastructure has a large percentage of false positives, so the study of ciliary motility should be considered the gold standard for diagnosis.

PS13
Is spirometry less accurate than chest computed tomography in primary ciliary dyskinesia with pulmonary deterioration?
Marco Maglione 1, Andrew Bush 2, Silvia Montella 1, Carmine Mollica 3

Is pulmonary deterioration a reliable marker of clinical deterioration in PCD and is spirometry less accurate than chest computed tomography in primary ciliary dyskinesia (PCD) associated with pulmonary deterioration? Spirometry was compared with chest computed tomography (CT) scans of 40 patients with documented pulmonary deterioration between February 2007 and December 2008. CT scans were scored blind by two experienced raters.

Results: Patients were divided into two groups based on the presence or absence of pulmonary deterioration. In PCD patients with pulmonary deterioration, spirometry may fail to detect worsening CT findings. Structural changes may progress with stable pulmonary function. CT scans are a useful tool to evaluate the course of the disease.

PS14
Changing characteristics of childhood non-cystic fibrosis bronchiectasis
Ela Erdelen 1, Yasemin Gokdemir 2, Recep aErsu 2, Fazilet Karakoc 2

In developing countries, characteristics of the chronic diseases may change in time because of changes in socioeconomic and health conditions. Our study aim was to evaluate the changing characteristics of non-CF bronchiectasis compared to our previous study (Karadag B. et al., Respir Res 2005:7:233-8).

Patients with non-CF bronchiectasis diagnosed two years ago and followed up after 2001 were recruited into the study. Long-term follow up records and lung function tests were used to evaluate the course of the disease. Collected data were compared with our previous data.

Of 100 patients included to the study, 54% were male. There was an increase in the mean age of the patients compared to our previous data (12.7±4.3 vs 7.4±3.7 years, p<0.005). During of symptoms was longer (6±3.7 vs. 4.9±3.7 years, p<0.005). As similar to the previous data, in 41% of the patients no underlying etiology could be detected. There was a change in the percentages of the detected etiology (2011 vs. 2001); postinfectious (21% vs. 29.7%, 0.01), asthma (12% vs. 4.5%, 0.07), immuredeficiency (12% vs. 15.3%, p=0.55), primary ciliary dyskinesia (1 vs. 6.3%, p=0.32) and foreign body aspiration (1 vs. 3.6%, p=0.37). During the follow-up period, in 25% of the patients the severity of the bronchiectasis improved. The rate of surgical management decreased from 23.4% to 9% compared to previous data (p=0.005).

Clinical characteristics of childhood bronchiectasis seems to be changing in a 10-year interval. There is a tendency for a decrease in the prevalence of postinfectious bronchiectasis however uncontrolled asthma and primary ciliary dyskinesia seems to be increasing. Surgical management is used only for a small group of patients.
78. Asthma: a heterogeneous disease

P519 Rasch analysis for evaluating abbreviated World Health Organization quality of life questionnaire (WHOQOL-Bref) in north Indian patients with bronchial asthma
Ashutosh Aggarwal, Ritesh Agarwal, Dheeraj Gupta. Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Introduction: A disease-specific instrument to describe health-related quality of life (HRQoL) in Indian asthmatics is not available. A generic Hindi HRQoL measure - abbreviated World Health Organization Quality of Life questionnaire (WHOQOL-Bref) - has however been developed and validated in India. We evaluated the WHOQOL-Bref in adult patients of asthma, and tested possible modifications to the instrument to improve its psychometric adequacy.

Methods: 67 asthmatics completed the WHOQOL-Bref. Rasch analysis was used to explore the psychometric performance of the four domains (physical, psychological, social relationships, and environment) of the scale. Overall fit of data to model expectations, appropriate category ordering, presence of differential item functioning (DIF), individual item fit, and targeting of item difficulty to patient ability were explored for each domain. Item deletion and rescoring were applied to misfitting items to improve overall performance.

Results: Overall fit of the WHOQOL-Bref data was adequate. Item 3 had a large positive fit residual value resulting in poor construct validity for physical domain. No item exhibited DIF. Ten items had distorted thresholds. The WHOQOL-Bref was modified by dropping item 3, and rescoring category structures of 16 items. The modified scale had good construct validity for all domains, ordered thresholds for all items, and good targeting of items to persons.

Conclusion: WHOQOL-Bref proved a psychometrically inadequate scale in our study group. However, the scale, when modified through Rasch analysis, proved better at describing HRQoL in the asthmatics studied.

P520 Lung sound monitoring in real time operation mode in diagnosis of exercise-induced asthma
Elena Kolganova, Sergey Glotov. Department of Postgraduate Education in Internal Medicine, Ryazan Medical University, Ryazan, Russian Federation

Introduction: Exercise-induced asthma is an actual problem of pulmonology and sports medicine. It is important to watch lung sounds evolution on physical activity.

Objective: Assessment lung sounds evolution and detection wheezes on physical activity.

Materials and methods: Clinical trial was conducted on 13 patients with diagnosis of bronchial asthma. The sensor of the electronic stethoscope was connected with the radio transmitter and placed at the patient’s neck over the trachea. Lung sounds were monitored at the field testing. The investigators got a lung sounds by radio receiver and analyzed it by computer program in real time operation mode.

Results: Wheezes were registered in 6 patients on physical activity. Wheezes appeared again on the 12-th minute after the end of the field testing in 2 patients. The following changes in the form of an acoustic pattern were observed in all patients: amplitude of an acoustic signal and frequency of respiratory cycles were increased, a respiratory cycle was shortened.

Conclusion: The use of lung sound monitoring in real time operation mode makes it possible to assess lung sound evolution and to detect wheezes during the field testing.

P521 Relationship between bronchial asthma and pelvic organ prolapse
Ismail Onderzra1, Ayse Ele Arcan2, Mustafa Albayrak1, Ismet Budun2, Ege Gulce Balbay4. 1Gynecology, Duzce University, Duzce, Turkey; 2Gynecology, Nesehri State Hospital, Nesehri, Turkey; 3Chest Diseases, Uludag University, Duzce, Turkey; 4Chest Diseases, Duzce Ataturk State Hospital, Duzce, Turkey

Objective: Genital organ prolapse is frequently observed in clinical practice. Vaginal birth, multiparity, menopause, history of genital prolapse, obesity, consol- idation and bronchial asthma are the most common determinants of risk of genital prolapse. The aim of the study was to evaluate the relationship between bronchial asthma and pelvic organ prolapse.

Materials and methods: A total of 200 patients, 100 bronchial astma, 100 control group were included in this study. Women, who were pregnant, in the period of 6 months after birth, having connective tissue diseases, had surgery for genital prolapse before and operative births in the past were excluded from the study. There was no limit in the age. Pelvic examinations were performed by using POP-Q system.

Results: There was a decrease in the measurements of the points Aa, Ba and C in the group of asthma bronchiola. There was no significant difference between the measurements of other points. Compared with control group, the stage using cost of care was £11,116 between the RSV and non respiratory groups (p=0.001) and £9,076 between the RSV and the other respiratory groups (p=0.007).

Conclusion: In infants born between 32-35 weeks of gestation, hospitalisation for an RSV LRTI was associated with significantly increased health related cost of care in the first two years after birth.
Background: The incidence and complexity of asthma acute exacerbations (AA) are widely increasing. The emergency physician (EP) plays a key role in AA: emergency department management; medical treatment; diagnosis; prevention; maintenance; follow up; education about self-management.

Aims: To define the epidemiological and clinical impact of AA at presentation to the emergency department (ED) and the role of the EP.

Methods: Six months observational prospective clinical study including every consecutive AA patient who presented to the ED of a university teaching hospital. Results: 209 patients were included (1:1.5 days).

Results: Parallel to the EP's recommendations during the year; the 2nd group included the patients with negative compliance (NC), they either absolutely or partially did not follow the recommendations. The patients with NC had a more intense degree of BA severity (69%) and were of an older age (p<0.002). Higher values were revealed in the 2nd group by TAS, scales of depression, personal and reactive anxiety. The average profile of a personality by MMPI scales in BA patients with NC was higher than the standard one. A high risk of psychopathologic reactions was revealed in the patients of this group (impulsiveness, nonconformity, nonstereotypeness). The patients of this group had inner tension, nervousness, aloofness, which can be a predictor for bronchial asthma.

Conclusion: For BA patients with NC it is necessary to create a psychotherapeutic environment in the hospital as well as an individual approach to recommendations and their explanation.

P526 Glucocorticosteroid receptor (GCR) gene isoforms expression in bronchial asthma (BA) patients

Zhanna Mironova1, Vasily Trofimov1, Vasily Belash1, Elena Ianchitsa2, Anna Ultina2, Michael Dubina2. 1Hospital Therapy, I.P. Pavlov Medical State University, St. Petersburg, Russian Federation; 2Molecule and Gene Technologies, I.P. Pavlov Medical State University, St. Petersburg, Russian Federation

Peculiarities of GCR function is one of mechanisms of steroid dependent asthma (SDIA). Most important isoforms are CRα and CRγ, formed due to alternative splicing of NR3C1 gene. Alternatively to CRα, CRγ is not linked to glucocorticosteroids (GCS), acting as an inhibitor, which concur with CRα for linking with hormone responding element or coactivator. This mechanism may lead to steroid resistance (SR).

The aim of study was to evaluate the role of GCR isoforms in SDIA development. Methods: 9 SDIA patients, 15 ones – with mild asthma (MBA), 7 – moderate BA and 7 healthy controls were included. In 10 MBA ones, inhaled GCS were primary administered. In this group blood samples were taken before and 2 weeks after of treatment. In SDIA patients, having long history of inhaled and oral GCS, blood was taken once. Total RNA from peripheral blood cells was isolated using RIBO-zol-B nucleic acid extraction kit (CRIE, Russia). Level of CRα and CRγ expression was evaluated by RT-PCR method. Results: No statistic difference between expression levels in BA and controls was found. CRα expression was higher in SDIA than in other asthmatics (243.0 ± 30.7; p=0.05). In MBA during the GCS treatment trend to CRγ expression increase (from 9.3 to 94.5) and CRγ expression decrease (from 82.9 to 33.3) was revealed. Significantly increased CRα/CRγ ratio in MBA after treatment (from 0.5 to 17.7; p=0.022) was same as in SDIA (19.9).
**Introduction:** Asthma, as a public health problem world-wide, seems to be significantly associated with GERD. GERD and its symptoms are also more prevalent in pregnant women, worsening by the increase in gestational age. This study aimed to evaluate GERD and its relation to asthma in pregnant women.

**Methods:** One-hundred and seventy three pregnant women (mean age, 28.8±5.3 years and mean gestational age, 24.8±6.9 weeks) were included. The diagnosis of asthma was made on the basis of the Guidelines of the National Asthma Education and Prevention Program (NAEPP). As challenge tests are not recommended in pregnancy, a group of patients were classified as probable-asthmatics. They were the ones who had asthmatic symptoms and signs suggestive of asthma but the spirometry was normal.

**Results:** Asthma was diagnosed in 37% of the included women and 26.6% were probable to have asthma, while 36.4% were non-asthmatics. GERD was present in 80.9% of the pregnant women. GERD was not significantly higher in asthmatic or probable asthmatic women compared to non-asthmatic ones, but in pregnant women who had asthma, GERD was significantly more severe compared to women who did not have asthma (p=0.02).

**Conclusion:** In this study, we observed a high prevalence of GERD in pregnant women. Although GERD was not higher in asthmatic or probable asthmatic pregnant women, it tended to be more severe in asthmatic cases. This points to the importance of early diagnosis and treatment of GERD in asthmatic pregnant women.

---

**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Coexist</th>
<th>Coexist</th>
<th>Not coexist</th>
<th>Not coexist</th>
</tr>
</thead>
<tbody>
<tr>
<td>No A</td>
<td>100</td>
<td>74</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Mild A (int)</td>
<td>32</td>
<td>24</td>
<td>75,0</td>
<td>12</td>
</tr>
<tr>
<td>Mild A (pers)</td>
<td>42</td>
<td>24</td>
<td>57,1</td>
<td>18</td>
</tr>
<tr>
<td>Moderate A</td>
<td>28</td>
<td>16</td>
<td>42,9</td>
<td>12</td>
</tr>
<tr>
<td>Severe A</td>
<td>5</td>
<td>3</td>
<td>33,4</td>
<td>2</td>
</tr>
<tr>
<td>A = No</td>
<td>11</td>
<td>8</td>
<td>27,3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Results:** Placenta development coexisted terms of gestation in 72% of pregnant, administered ICS and in only 45.8% of A pregnant, rejected ICS intake (p=0.011). Significant differences of chronic placental insufficiency were seen between pregnant with the mild intermittent A and mild persistent BA, as well as with moderate chronic (35.38, 51.2% and 71, 4% resp (p<0.05)). Within pregnancies, administered ICS 70% appeared compensated, 25.93% - sub compensated and 7.07% decompenesed placental insufficiency. Within patients, rejected ICS values were 47.14%, 45.71% and 7.15% respectively.

**Conclusions:** Treatment with ICS while pregnancy has greater influence to placenta condition in comparison with A severity.

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**P351**

**Impact of smoking in patients with and without history of asthma**

Ileana Palma, Pável Escina, Raquel Aguirre, Maria Rolando, Daniel Antuni, Ricardo Gene.

**Pulmonary Division, Hospital de Clinicas Jose de San Martin; Universidad de Buenos Aires, Buenos Aires, Caba, Argentina**

Patients with a history of asthma who smoke develop an accelerated decline in lung function and greater mortality. More complex studies are needed to distinguish asthma from COPD in this population.

**Objectives:** Evaluate the characteristics of a COPD population with and without history of asthma.

**Methods:** We invited people ≥ 40 y/o who smoked at least 10 years (current or ex-smokers), during one week on Nov 2005, 2007/2009. A questionnaire on respiratory symptoms, demographics and spirometry were done. COPD was defined by a FEV1/FVC < 70, the presence of symptoms and smoking history. Population was divided into 2 groups: COPD with history of previous asthma (AS) and COPD (NAS).

**Results:** 1626 patients were surveyed; 61 were excluded (< 40 y/o or non-obstructive lung disease). Mean age was 58.4±10.4 y/o. 54% were men. 89% patients had previous diagnosis of asthma. 329 of 1565 (21%) patients were diagnosed with COPD, 42% of AS vs 19% of NAS (p=0.001). The pack/year index in AS was 19±10 vs. 34±23 in NAS (p = 0.001). FEV1 (% and FEV1/FVC were comparable in both groups (67% and 57 vs 59). No differences in symptoms was found (p> NS) AS had more emergency visits (39.5% vs 24.4%, p = 0.047),
higher previous spirometric tests (73.7% vs 54.6%, p = 0.026) on the last year, and higher use of bronchodilators and ICS.

| Table 1 |
|-----------------|-----------------|-----------------|
| AS (n=58)       | NAS (n=291)     | p                |
| Salbutamol      | 12 (31%)        | 40 (13.7%)       | 0.039 |
| Ipratropium     | 3 (7.8%)        | 15 (5.1%)        | 0.78  |
| LABA            | 8 (21%)         | 27 (9.2%)        | 0.10  |
| ICS             | 14 (36.8%)      | 45 (15.5%)       | 0.02  |
| Oral Steroids   | 2 (5.2%)        | 1 (0.3%)         | 0.046 |

Conclusions: Patients with history of asthma develop COPD more often, with lower smoking load, and have higher use of medical resources in spite of more use of effective treatment.

P534
Self-reported dental health and related factors in patients with asthma and chronic obstructive pulmonary disease
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Background: There are some studies about dental problems of asthmatic patients. However, studies comparing dental diseases in patients with asthma and with COPD are not sufficient.

AIM: Our aim is to compare the frequency of self-reported dental problems, their treatments and to determine affecting factors.

Method: A face-to-face questionnaire including the history of their diseases, dental problems and treatments, tooth brushing habits and comorbidity questions was applied by a doctor to the patients who admitted to Chest Diseases Dept. and Immunology and Allergy Diseases Subdept.

Results: 292 patients (63.4% asthmatic, 36.6% with COPD) and 286 controls were included to the study. Mean dental disease durations were 14.04±6.80 and 15.18±1.01 years in patients with asthma and COPD, respectively (p<0.05). There were dental problems in 91.6% of asthmatics and in 97.8% of COPD patients (p=0.01). The frequency of the subjects with dental caries was 89.7% in asthmatics, 95.3% in COPD patients, and 86.4% in the control group (p=0.04). As for tooth brushing habit, 47.0% of asthmatic patients, 21.5% of patients with COPD, and 58.0% of the control group stated to perform regularly once or twice per day (p<0.001). Only 41.6% of asthmatic patients, 9.3% of COPD patients, and 52.1% of control group (p<0.001) had elementary or higher education.

Conclusions: Dental caries is the most frequent dental problem. The frequency of tooth brushing is related to the educational status and the patients should be instructed to perform this act regularly as recommended.

79. COPD management

P535
Inhibiting effects of tiotropium bromide on neocollagenesis during 6 month treatment
Mykola Ostrovskiy, Oleksandr Varukiv, Mariana Kulynych-Misik, Iryna Savelikhina. Internal Medicine, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Background: Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality worldwide, which are the third most common cause of death (8%) in the 25 member states of the European Union.

Purpose of the study: Is the evaluation of type IV collagen dynamic in bronchoalveolar lavage (BAL) during the treatment with tiotropium bromide.

Materials and methods: The content of type IV collagen was investigated in BAL of 43 control patients with stage 2 COPD before and after 1,3 and 6 months of treatment with tiotropium bromide using ELISA.

Results of the study: The content of type IV collagen in BAL on a moment of hospitalization in patients with COPD exacerbation was (61,14±1,28) ng/ml that is in 6.19 times (p<0.05) higher than in healthy. In patients with COPD exacerbation treated within 1 month with integrated treatment including tiotropium bromide as a basic therapy we identified the reduction of type IV collagen levels in 1.41 times in BAL compared with data before treatment. We found further positive trends - reduction of type IV collagen on 79.4% with using tiotropium bromide within 2 months. The level of type IV collagen in bronchoalveolar fluid dropped in 2.23 times (p<0.05) compared with the level before treatment. We identified practically complete normalization of type IV collagen levels in BAL only during 6-month of tiotropium bromide admission in patients with stage 2 COPD. This rate was higher only at 29.8% (p<0.05) comparing with healthy.

Conclusions: The reduction of type IV collagen content in BAL under tiotropium bromide treatment during 6 month is a clear evidence of inhibiting effects of tiotropium bromide on neocollagenesis.

P536
Effect of erdosteine on airway obstruction and symptom recovery in severe COPD exacerbations
Maurizio Moretti, Maria Ballabio. Respiratory Medicine, ASL1 Massa e Carrara, Carrara, Italy; 2Medical Department, Edmond Pharma, Milano, Italy

Introduction: Acute COPD exacerbations (AECOPD) represent an important cause of morbidity and mortality. Early and effective interventions may improve their outcome and patients’ health status.

Objective: This study evaluated the effect of erdosteine, an anti-oxidant mucolytic agent, on airflow limitation and symptom recovery at AECOPD

Methods: 15 COPD patients hospitalized for an acute exacerbation randomly received erdosteine 900 mg daily (E) or placebo (P) for 10 days in combination
with standard steroid, antibiotic and bronchodilator treatment. Pulmonary function test including spirometry (PVC, FEV1, FEF25–75) and breathlessness, cough, and sputum scale (BCSS) were measured at hospital admission, and at 10 and 30 days post-exacerbation.

Results:

<table>
<thead>
<tr>
<th>Time</th>
<th>FEV1 ml</th>
<th>% pred</th>
<th>PVC ml</th>
<th>% pred</th>
<th>FEF25–75 ml/sec</th>
<th>Symptoms score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endosine</td>
<td>Baseline</td>
<td>1201</td>
<td>48.0</td>
<td>2667</td>
<td>58.7</td>
<td>457</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td>1050</td>
<td>67.0</td>
<td>2668</td>
<td>70.9</td>
<td>639</td>
</tr>
<tr>
<td></td>
<td>30 days</td>
<td>1574</td>
<td>67.4</td>
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<td>811</td>
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<td>Placebo</td>
<td>Baseline</td>
<td>1142</td>
<td>44.8</td>
<td>2058</td>
<td>61.3</td>
<td>335</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td>1218</td>
<td>45.6</td>
<td>2315</td>
<td>64.9</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td>30 days</td>
<td>1288</td>
<td>50.2</td>
<td>2470</td>
<td>71.6</td>
<td>472</td>
</tr>
</tbody>
</table>

*p<0.05 and **p<0.01 vs. P.

The improvement of lung function parameters and symptom scores from baseline was significantly greater in patients receiving endosine. Symptom score recovery significantly correlated to improvement of airway obstruction at time 10 and 30 in the erdosteine group.

Conclusions: Treatment with endosine plus standard therapy in AECOPD proved to be effective in improving both clinical symptoms, and large and small airway impairment. Mucoytic agents with relevant antioxidant activity may allow a more rapid and complete recovery of exacerbated patients by reducing the burst of airway inflammation.

P537

Analysis of therapy of community-acquired pneumonia (CAP) at the COPD patients

Hanna Demchuk, Yurii Mostovoy.

To assess extent, accuracy and efficiency of therapy of CAP at patients (PT) with COPD case histories of 252 inpatients (54.4% males, mean age 59.03±13.7 years) admitted due to CAP and COPD exacerbation were analyzed. PT with non-severe CAP were 94.8%. Moderate COPD had 54.4% PT, severe COPD – 34.1%, very severe COPD - 4%. Cardiovascular diseases were more than 60% PT. Analysis of therapy revealed average amount of prescribed medicines was 17.2±3.2. The most frequently used antibiotics was cephalosporins of third generation (61.9%), macrolides (21.4%), ciprofloxacin (20.6%) and inhibitor-protected aminopenicillins (14.3%). Correct combination of beta-lactam+macrolide was prescribed 40.2%. Combinations of fluoroquinolone with beta-lactam received 12.1% or fluoroquinolone+aminac in 7.5%. These combinations are alternative treatment for investigated PT. Non-recommended antibiotic therapy received 18.6%. Amoxicillin/clavulanate +macrolide, cefixim+n macrolide and ciprofloxacin+beta-lactam or aminac was the most effective treatment (in 99.6%, 95.0% and 95.2% PT, relatively). For exacerbation the erdosteine group.

Conclusions: The improvement of lung function parameters and symptom scores from baseline was significantly greater in patients receiving erdosteine. Symptom score recovery significantly correlated to improvement of airway obstruction at time 10 and 30 in the erdosteine group.

P540

Polypharmacy in patients with acute exacerbation of COPD

Jesús Díez-Manglano1, Jesús Reaco-Iglesias2, F Javier Cabrera-Aguilar3, ECCO Study Investigators1, 1COPD Working Group, Spanish Society of Internal Medicine, Zaragoza, Badajoz, Tarrasa, Barcelona, Madrid, Spain; 2Fundación Cuadet-Cimera, Fundación Cuadet-Cimera, Banyola, Mallorca, Spain

Introduction: Polypharmacy (PP) is frequent in patients with COPD who often have comorbid chronic diseases, and PP increases the risk to experience adverse drug events.

Objective: To determine the prevalence of PP in patients hospitalized for an acute exacerbation of COPD, and the factors associated with PP in this population.

Subjects and methods: ECCO is an observational, prospective, multicentre study. It included those patients admitted with a COPD exacerbation to any of the participating Internal Medicine departments consecutively between January 1, 2007, and December 31, 2008. They were all spirometry-confirmed COPD GOLD II or higher in stable condition. PP was defined as chronic concurrent use of ≥5 medications and excessive PE (EPP ≥10).

Results: 398 patients, 353 men and 45 women, with a mean (SD) age of 73.7 (8.9) years were surveyed. The average use of drugs was 5.0 (2.6). On admission 224 (56.3%) had PP and 22 (5.6%) EPP. Patients with PP had more comorbidity (Charlon index 2.8 (2.8) vs 2.3 (1.6); p=0.004) and more severe mBSC dyspnea (p=0.009) but there were no differences according to GOLD stage. On discharge the average chronic use of drugs was 6.6 (2.4) in an increase in 272 (68.3%) patients. At discharge, 296 patients (78.7%) had PP and 44 (15.9%) EPP. Patients with PP at discharge had more comorbidity and lower FEV1 (<p=0.001). In a multivariate logistic regression model PP was associated with lower predicted FEV1, heart failure, hypertension, diabetes, home oxygen therapy and PP on admission.

Conclusions: Polypharmacy is frequently observed in COPD patients, and is associated with more severity of COPD and more comorbidity.

P541

Comparison of two models of factors associated to hospital admission for COPD

Bernardinó Alcázar Navarrete1, Alberto Herrejón Silvestre2, Cayo García Polo3, Luis Alberto Ruiz4, Patricia García Sidro5, Gema Tirado Conde6, Jose Antonio Los Lucas7, Carlos Martínez Riveraa8, Joaquín Costán9, Sagarnag Mayoralas10, Marc Miravitlles11, InEPOC Group11.

Aim of the study was to determine the current incidence of pulmonary complications and management of patients with chronic obstructive pulmonary disease.

Nina Karoli, Andrey Rebeyko.

Hospital Therapy Department, Saratov State Medical University, Saratov, Russian Federation

The incidence of cardiovascular complications at admission due to exacerbation of COPD in patients with COPD III-IV stage PP was 20.2 times less often than in patients with COPD I-II stage. Difference in severity between survivors and those which died was significant (p<0.001)
Introduction: COPD is a leading cause of hospital admissions.

Objectives: We aimed to identify factors significantly associated with hospital admission in patients with COPD. Demographic and clinical data, treatment and socioeconomic status were collected. Evaluation of comorbidities (Charlson index), psychological profile (HAD questionnaire), health-related quality of life (EuroQOL-5D, LCADL), pulmonary and cardiac function testing, 6MWT and BODE index were measured and compared between patients with and without hospital admission the last year.

Results: 127 patients were included, of which 50 (39.3%) were hospitalized the previous year. Patients hospitalized for COPD exacerbations showed more use of Emergency Room, LITOT, NIVM, worse SpO2, and PVC, and worse BODE and EuroQol scores. The findings from the multivariate analysis made possible to establish two models: the one with SpO2, BODE index, and previous visits to ER had a sensitivity of 64.2% and a specificity of 86%.

Conclusions: SpO2 and the presence of previous hospital admissions are associated with worse SpO2, BODE index, baseline MRC and previous visits to ER department. If 6MWT is not available, the other variables provide a similar discrimination capacity between admitted and non admitted patients.

P542 More than two years of a monographic consultation on control of chronic home oxygen therapy

Teresa Bilbao Goyago, Natividad Quiñez, Lorena Comeche, Dolores Alvaro, Juan Manuel Diez, Raquel Perez. Pulmonology Department, Mostoles Hospital, Mostoles, Madrid, Spain

Objectives: To know the characteristics of our patients on chronic home oxygen therapy. We assess the prescription criterion, the prescriber department, time since diagnosis of the patients, the duration of the consultation and the number of consultations per patient.

Materials and methods: Retrospective descriptive analysis of the patients that attend to our monographic consultation since it started on October of 2008.

Results: The number of patients is 598 with 1181 number of consultations, this represents 17,5% of the total number of patients. The most frequent diagnoses in patients control, p<0.05), reduced the number of neutrophiles (24,8±5,9% vs 32,1±5,7% in patients control, p<0.05) and significantly reduced the level of pro-inflammatory cytokines, especially the level of IL-8 (23,4±6,5 µg/ml vs 38,9±7,8 µg/ml in patients control, p<0.05). Considered significantly efficacy on lung function, on cell and cytokine contents of induced sputum, we can conclude that, low doses of theophylline as the PEI inhibitor may improve steroid sensitivity and to be approved for the management in patients with ever COPD.

P544 The influence of high doses of N-acetylcysteine alone or in combination with inhaled corticosteroids on quality of life in patients with COPD

Valentina Kapustina, Svetlana Ovcharenko. Faculty Therapy No.1, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

Background: The aim of our study was to evaluate the effects of 6-month oral N-acetylcysteine (NAC) treatment 1200 mg/day alone or in combination with inhaled corticosteroids (ICS) on health-related quality of life (QOL) in outpatients with COPD.

Methods: A total of 62 patients with stable COPD (36 males, mean age 66.8 years, GOLD stage I-IV) were included and divided into two treatment groups. Group 1 received NAC 1200 mg/day alone or in combination with inhaled corticosteroids. Group 2 was treated with standard ICS. Differences in baseline characteristics were tested using chi-square or t-tests. Data were analyzed using SPSS version 11.0.

Results: During a 15-month follow-up, we observed significant improvements in QOL measured both SF-36 and SGRQ with greater changes in combination therapy. We assess the prescription criterion, the prescriber department, time since diagnosis of the patients, the duration of the consultation and the number of consultations per patient.

Conclusions: Long-term treatment of stable COPD patients with NAC 1200 mg/day improves QOL measured both SF-36 and SGRQ with greater changes in combination of NAC with ICS.
The link between COPD and atherosclerosis (AS) has been speculated but such information at clinical features of COPD and its relation to AS is limited. To evaluate subclinical AS in patients with COPD 33 male COPD patients and 15 healthy male control subjects included the study. Subjects with exacerbation, DM, chronic renal failure, cardiac diseases excluded. All the subject underwent spirometry, blood sampling, carotid artery USG, 24 hour oxygen saturation recording via a holteroxymeter. We determined carotid artery intima-media thickness (CAIMT) as indicator of subclinical AS. Mean CAIMT was greater in COPD group (p=0.005) with regard to the cardiac evaluation, the physical examination (yugular venous distention: 21.1% vs 4.6%; p=0.017), the ECG (28.9% vs 10.8%, p=0.030), the distention: 21.1% vs 4.6%, p=0.017; peripheral edema: 31.6% vs 12.3%, p=0.022, the systolic BP, mmHg 130.1 ± 19.9 vs 118 ± 16.1, p=0.03. The diastolic BP, mmHg 79.7 ± 11.9 vs 72.6 ± 6.6, 0.009. CRP mg/L 6.04±4.5 vs 3.4±1.8, p=0.03. % FEV1 44.1±7.5 vs 19.1±18.3, p<0.001. % FVC 57.2±14.6 vs 104.0±15.3, p<0.001. Average saturation in 24 hours 90.8±3.7 vs 94.9±1.2, p<0.001. % FVC 32.3±10.8 vs 34.2±10.1, p<0.001. Mean CAIMT 0.802±0.19 vs 0.65±0.07, p=0.005. HsCRP: High sensitive CRP, T90%: Time below 90% saturation.

Table 2. Pearson's correlation of all subjects for CAIMT and other variables.

<table>
<thead>
<tr>
<th>Coefficient number</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.39</td>
</tr>
<tr>
<td>Duration of COPD</td>
<td>0.304</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.444</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.353</td>
</tr>
<tr>
<td>T90%</td>
<td>0.320</td>
</tr>
<tr>
<td>CRP</td>
<td>0.32</td>
</tr>
<tr>
<td>% FEV1</td>
<td>-0.343</td>
</tr>
</tbody>
</table>

Multivariate stepwise analysis showed significant associations between CAIMT and decreased % FEV1 (p=0.018) and between systolic BP (p=0.004) independent of age, BMI, duration of illness, diastolic BP, % FVC, CRP. T90%. Although the duration of COPD, T90% and CRP correlated with CAIMT, impaired lung function and severity of systolic blood pressure the predict CAIMT.

Multivariate stepwise analysis showed significant associations between CAIMT and decreased % FEV1 (p=0.018) and between systolic BP (p=0.004) independent of age, BMI, duration of illness, diastolic BP, % FVC, CRP. T90%. Although the duration of COPD, T90% and CRP correlated with CAIMT, impaired lung function and severity of systolic blood pressure the predict CAIMT.

Conclusions: 1. The global prevalence of HD in our cohort of patients with an acute exacerbation of COPD was 37%. 2. In this setting, physical examination, an abdominal ECG, an EF<50% and a NT-proBNP value > 1200pg/mL could help to identify patients with a probable HD. 3. Fifty-six-six of readmissions were patients in GOLD stage IV.
Results: Results are presented in the Table.

| Parameter | Before Treatment | After Treatment | p  
|-----------|-----------------|----------------|------
| Cough     | 1.27±0.14       | 0.64±0.15      | 0.004
| Mucus     | 0.91±0.21       | 0.36±0.15      | 0.038
| Breathlessness | 1.91±0.16  | 1.00±0.19      | 0.001
| FVC (% pred) | 84±5.86       | 93±3.65        | 0.361
| FEV1 (% pred) | 53±4.52       | 68±4.89        | 0.214
| FEV1/FVC  | 0.53±0.04       | 0.56±0.05      | 0.501
| PEF (% pred) | 50.4±4.21     | 63.0±5.14      | 0.117
| SBG: symptoms score | 61.7±3.10     | 61.6±4.05      | 0.000
| SBG: activity score | 53.6±8.33     | 47.7±8.03      | 0.613
| SBG: impacts score | 42.4±9.97     | 42.0±11.9     | 0.814
| SBG: total score | 48.7±6.13     | 42.8±6.07      | 0.482

P553

Evaluation of incontinence and quality of life in patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis

Claire Brockwell, Ailian Clark, Alexandra Baker, Ben Hacker, Gabriella Pardo, Helen Little, Andrew Wilson. School of Medicine, University of East Anglia, Norwich, United Kingdom

Background: Incontinence is common and more prevalent in respiratory disease. Despite this, the effect of incontinence on quality of life in respiratory patients is unknown.

Methods: We conducted a case controlled questionnaire study. We sent the International Consultation on Incontinence Modular Questionnaire (ICIQ), the Leicester Cough Questionnaire (LCQ), the EuroQol 5D (utility) and the MRC questionnaire to 150 patients with COPD, 150 patients with bronchiectasis and 150 controls (orthopaedic surgical patients). The groups were age and gender matched. Mann-Whitney test was used to determine effects of gender and disease.

Results: 164 (81 male) patients and 53 (22 male) controls replied. Overall, females (68%) had more incontinence than males (41%). Median (IQR) values for ICIQ were significantly (p=0.05) higher for female patients (4 (0-7.5)) but not for male patients (0 (0-4)) compared to controls (3 (0.5-5.5), 0 (0-3.7) respectively). However, male, but not female, patients with incontinence had a significantly (p=0.01) lower utility score, despite no difference in MRC (table).

Effect of incontinence on quality of life

<table>
<thead>
<tr>
<th>Gender</th>
<th>ICIQ*</th>
<th>Utility*</th>
<th>LCQ*</th>
<th>MRC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>23</td>
<td>72.7±10.4</td>
<td>0 (0-7.0)</td>
<td>17.4±13.8</td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>67.6±10.7</td>
<td>0 (0-6.9)</td>
<td>14.8±9.0</td>
</tr>
</tbody>
</table>

Values as median (IQR).

Conclusion: Incontinence is more common in females but males with incontinence had more impaired overall health related quality of life.

P554

Initial clinical phenotype of COPD: Correlation with the natural history of the disease

Luca Fasano¹, A.M. Grazia Pacilli², Paolo Carbonara³, Valerio Di Sciascio³, Haria Valentini¹, Giacomo Miste², Angela Montanari³, Mario Fabbrè³, Maurizio Zompatori³, Stefano Nava³. Respiratory and Critical Care Unit, S Orsola Malpighi University Hospital, Bologna, Italy; ²Cardiothoracic Radiology, S Orsola Malpighi University Hospital, Bologna, Italy; ³Statistics, University, Bologna, Italy

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Aim of this study was to evaluate, at the time of the first specialist evaluation, the differences in lung and cardiac function and HRCT extent of emphysema in patients with a spirometric diagnosis of COPD but different initial clinical presentation (chronic bronchitis [CB] versus dyspnea [Dy]). 45 consecutive patients referred to our outpatients service by their GP were divided according to their main first symptom (chronic bronchitis or dyspnea). Patients with Dy had an obviously higher dyspnea score vs those with CB (MRC 2.9±0.9 vs 2.3±0.6, p=0.02) and produced much less sputum (p=0.001). The severity of obstruction was similar in the two groups (FEVI 31±11% predicted in both groups, p=0.89; FEVI/FVC 26±6% vs 27±7%, respectively for Dy and CB, p=0.62). The CB had worse arterial blood gases (PaO2 62±12 vs 69±10 mmHg, p=0.03; PaCO2 50±7 vs 45±7 mmHg, p=0.02) and showed a higher proportion of pulmonary artery diameter >29 mm (a surrogate sign of pulmonary hypertension) 18/24 vs 8/21 pts, p=0.02). Dy group had larger CT emphysema extension score (18 ± 5 vs 13 ± 6, p=0.06). In conclusion we have shown differences between the two COPD phenotypes with similar airflow limitation, with CB patients showing worst ABGS and indirect signs of pulmonary hypertension, while Dy group was characterized by a higher degree of emphysema.

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*Sundays, September 25th 2011

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Details of tables and statistical analyses are omitted for brevity.
P555
Relationships between elevated cardiac troponin levels in COPD exacerbations and subsequent cardiac investigation and management
Padman R. Vamadevan, Andrew W. Hitchings, Dana Almood, Tejwant S. Grewal, Emma H. Baker. Clinical Pharmacology Unit, Division of Biomedical Sciences, St George’s, University of London, London, United Kingdom

Background: Admission cardiac troponins (cTn) are elevated in 18-27% patients with COPD exacerbations (BMC Palm Med 2009;9:35). Clinicians often attribute this rise to co-existing inflammation, anaemia or renal impairment. However, elevated cTn is associated with a significantly increased 30-day post-admission mortality independently of these factors, and its presence indicates underlying myocardial injury. We determined proportions of patients undergoing cardiac investigation and receiving cardioprotective treatment following an exacerbation-related cardiac troponin I (cTnI) rise.

Methods: 237 COPD patients (127 male, 73±1±1lyrs) admitted with exacerbations between July 2008-9, and with a measured cTn within 24h of admission were retrospectively identified. Clinical information was retrieved using the electronic patient record.

Results: Admission cTnI was ‘undetectable’ (U, <0.02g/l) in 15%, ‘measurable’ (M, 0.02-0.05g/l) in 59% and ‘elevated’ (E, >0.05g/l) in 26% of patients.

<table>
<thead>
<tr>
<th>U</th>
<th>M</th>
<th>E</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations within 3 months of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>11%</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Cardiac Catheterisation</td>
<td>0%</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Discharge medication (n=205)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>40%</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>ß-blocker</td>
<td>7%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Statin</td>
<td>33%</td>
<td>42%</td>
<td>40%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>27%</td>
<td>26%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Conclusions: cTn elevation is not specific for coronary thrombosis, and rises in exacerbations may reflect demand ischaemia, direct cardiac damage, or myocardial strain. No guidelines exist regarding the optimal management of such patients. However, given their important risk of early mortality, further cardiac investigation to reveal underlying mechanisms of cTnI release may enable appropriate therapeutic targeting and improve outcomes.

P556
Comparison of multidimensional assessment systems with regard to risk prediction for exacerbations of COPD
Takashi Motegi1, Takeo Ishii1, Kumiko Xattori1, Koichiro Kamio2, Rana Bibi1, Lene Birket-Smith1, Søren Rismon Kristensen2, Stephen Edward Rees1, 2Pulmonary Medicine, Aalborg Hospital, Aalborg, Denmark, 3Clinical Pharmacology Unit, Division of Biomedical Sciences, St George’s, University of London, London, United Kingdom

Aim: Acute Exacerbations of COPD (AECOPD) are major concerns with regard to morbidity, mortality and economic burden. In this study, we compared the efficacy of 3 assessment systems for predicting AECOPD: BODE index (Body mass index, airway Obstruction, Dyspnea, Exercise capacity), DOSE index (Dyspnea, airway Obstruction, Smoking status, Exacerbations); and ADO index (Age, Dyspnea, airway Obstruction).

Participants and methods: The frequency of exacerbations (FE) for a 1-year period was retrospectively studied for 183 consecutive patients with COPD. Following parameters were used to compare the results: pulmonary function tests, 6-minute walking test, MMRC dyspnea scale, low-attenuation area (LAA%) on HRCT and FE.

Results: The study included 183 patients (M/F 170/13). The mean age and FEV1/spredicted were 71.4 years and 55.7%, respectively. The mean annual exacerbation rate was 0.57 per patient-year. FE was significantly correlated with the following parameters: lower FEV1/spredicted (p<0.01), lower DLCoVa (p=0.021), shorter 6MWD (p=0.016), higher MMRC (p<0.001), higher DOSE index (p<0.001), higher BODE index (p=0.001), higher ADO index (p=0.001), and larger LAA% (p=0.002). FE was significantly associated with prescribed long-term oxygen therapy (Odds ratio [OR] 4.17, p < 0.001) and exacerbation rate for the previous year (OR 2.79, p < 0.001). The area under the receiver-operator curve for predicting exacerbation during the 1-year follow-up was 0.65 for the BODE index, 0.64 for the ADO index, and 0.75 for the DOSE index.

Conclusions: The DOSE index appears to be superior to the BODE and ADO indices in terms of predicting exacerbation rate of COPD.

Conclusions: The method may be a useful tool to evaluate COPD patients during admission without the need for repeated arterial punctures.
### PS59

**Do exacerbation outcomes in the POET-COPD™ trial differ between regions?**

<table>
<thead>
<tr>
<th>Region</th>
<th>N Tiotropium / salmeterol</th>
<th>Tiotropium vs salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time to first exacerbation</td>
<td>Hazard ratio [HR] (95% CI)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2449 (2412)</td>
<td>0.87 (0.70-0.95)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>925 (926)</td>
<td>0.83 (0.72-0.97)</td>
</tr>
<tr>
<td>Nordic</td>
<td>70/75</td>
<td>0.81 (0.51-1.29)</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>263/256</td>
<td>0.81 (0.62-1.04)</td>
</tr>
</tbody>
</table>

*R* value: 0.05

**Aim and objectives:**

This was a post-hoc analysis to examine if geographical region influenced exacerbation outcomes.

**Methods:**

Inclusion criteria were age ≥40 years, postbronchodilator forced expiratory volume in 1 s (FEV1) ≥70% predicted and ≥1 exacerbation in prior year. Countries (n=25) were grouped into four regions: Eastern Europe, Western Europe, Nordic and Mediterranean. Interaction analyses were performed for time to first exacerbation (primary endpoint) and annual exacerbation rate.

**Results:**

7376 patients were randomized and treated. Results are shown in the table.

**Conclusions:**

Post-hoc subgroup analysis of the POET-COPD™ trial by geographical region suggests that the exacerbation benefits of tiotropium over salmeterol are independent of region.

Funded by Boehringer Ingelheim/Pfizer

### PS60

**Effect of acute exacerbations on circulating thrombotic and fibrinolytic markers in COPD patients**

**Method:**

Surrogate markers of inflammation were collected: interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, von Willebrand’s factor (vWF), platelet activation factor (PAI-1), in COPD subjects during exacerbation.

**Results:**

IL-6 (pg/mL) 4.95 (2.98, 7.95) 3.2 (2.38, 4.78) –35.4% 0.005

CRP (mg/L) 146.99 (121.26, 231.4) 122 (91.1, 160.2) –21% <0.001

D-D (ng/mL) 1575.51 (1175.23, 2081.25) 127 (111.25, 151.5) –29.4% <0.001

PAI-1 (mg/L) 11.35 (9.38, 14.28) 10.7 (8.48, 13.38) –5.7% 0.765

All values are medians (QR).

**Conclusions:**

COPD exacerbations are associated with endothelial activation and clotting initiation. This was not associated with a change in PAI-1, implying a defect in the fibrinolytic response to inflammation. The pro-thrombotic nature of COPD exacerbations appears to be mitigated by excessive fibrinolysis.
P563 Procalcitonin use in acute exacerbations of COPD
Thomas Medveczky, Mark Jackson. Department of Respiratory Medicine, The Primary Royal Hospital, Brighton and Sussex University Hospitals NHS Trust, Haywards Heath, Sussex, United Kingdom

Background: Procalcitonin (PCT) is a circulating marker that is elevated in infection and inflammation.

Methods: We determined the role of procalcitonin in acute exacerbations of COPD (AECOPD) using PCT. Patients were recruited from all four hospitals in a primary care trust.

Results: 223 patients were recruited with AECOPD, of which 48 had normal PCT (<0.3 ng/mL).

Discussion: PCT is a useful marker in the diagnosis of AECOPD.

Purpose: To investigate the role of PCT in the diagnosis of AECOPD.

P564 Characteristics of patients with chronic obstructive pulmonary disease (COPD) discharged from the emergency department – Improving the care pathway for acute exacerbations of COPD
Santino Capocci, David Turner, Robert Pitane, Myra Stern, Louise Restrick. Respiratory Medicine, Whittington Hospital NHS Trust, London, United Kingdom

Introduction: The aim of this study was to characterise patients with COPD who are discharged from the emergency department.

Methods: Retrospective analysis of patient records from the Whittington Hospital, London, for COPD exacerbations that required admission to hospital over a 12-month period.

Results: 223 patients were identified with COPD exacerbations, of which 132 were discharged from the emergency department.

Discussion: The results of this study will be used to improve the care pathway for COPD exacerbations.

P565 Impact of pneumonia on mortality and length of stay in patients hospitalized with acute COPD exacerbations
Siw Lillevik Andreassen 1, Erik Dyb Liaaen 2, Nikolai Stenfors 3,4, Anne Siw Lillevik Andreassen 1, Erik Dyb Liaaen 2, Nikolai Stenfors 3,4, Anne Hildur Heniksen 5,6.

1The Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway; 2Department of Internal Medicine, Aalesund Hospital, Aalesund, Norway; 3Department of Respiratory Medicine and Allergy, Östersund Hospital, Östersund, Sweden; 4Pulmonary Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; 5Department of Pulmonary Medicine, Trondheim University Hospital, Trondheim, Norway; 6Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

Background and aims: Pneumonia is a common complication in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (COPD).

Methods: Retrospective analysis of patient records from the departments of Internal Medicine and Respiratory Medicine in one Swedish and two Norwegian hospitals. The study included 1144 patients with pneumonia and acute COPD exacerbations.

Results: The mortality rate was 5.9% in patients with pneumonia and COPD exacerbations, compared to 0.7% in patients with COPD exacerbations without pneumonia.

Discussion: Pneumonia is a significant risk factor for mortality in patients with COPD exacerbations.

P566 Infectious factors influences on cytomorphic picture of bronchial biopsies at COPD exacerbation
Ekaterina Bukreueva 1, Gulnara Seitoiva 2, Raisa Pleshko 3, 1Therapy, Siberian Medical University, Tomsk, Russian Federation; 2Medical Genetics, Siberian Medical University, Tomsk, Russian Federation; 3Morphology, Siberian Medical University, Tomsk, Russian Federation

Purpose: To study the influence of infectious factors on the cytomorphic picture of bronchial biopsies in patients with COPD.

Methods: Retrospective analysis of patient records from the departments of Internal Medicine and Respiratory Medicine in one Swedish and two Norwegian hospitals. The study included 237 patients with COPD exacerbations and 237 controls.

Results: In patients with COPD exacerbations, the cytomorphic picture of bronchial biopsies was characterized by increased expression of inflammatory factors, goblet cell hyperplasia, and goblet cell hyperplasia.

Discussion: The results of this study will be used to improve the care pathway for COPD exacerbations.
bating patients showed decline in processing speed than stable patients or controls (p<0.01) (figure).

Conclusion: Over half of patients prior to discharge with exacerbation and a quarter of stable patients with COPD exhibited significant cognitive decline in processing speed. It is unclear if the decline was acute, chronic or reversible.

P568
Post discharge mortality in North Indian patients with exacerbation of COPD
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Background: Mortality rates at 2 years following discharge among patients with exacerbation of COPD have ranged from 2% to 49%. No mortality data is available for such patients from India, especially Kashmir, where COPD is common.

Objective: To determine the post discharge mortality rate and its determinants among patients with COPD hospitalized for acute exacerbation, in a 650-bedded tertiary care facility in Srinagar, Kashmir (India).

Methods: One hundred and fifty-one patients admitted with a diagnosis of acute exacerbation of COPD from October 2008 to October 2010 & discharged after treatment were followed prospectively for a period of 2 years for any deaths and recurrences of exacerbations. The relationship of mortality with potential patient factors was analysed statistically by employing multiple logistic regression analysis, Kaplan-Meier survival analysis and Cox regression.

Results: During a followup of two years following discharge, 39.7% patients died with the majority (34.4%) of deaths occurring during the first year. Risk factors associated with increased mortality included lower health status at discharge (SGRQ score > 60, p value < 0.001), GOLD stage 4 (p < 0.001), BMI < 18 kg/m2 (p value < 0.001), SaO2 < 90% at discharge (p < 0.001) and 6MWT distance of < 150 metres (p < 0.001). Frequency of exacerbations increased with increasing GOLD stage (p < 0.001).

Conclusion: Mortality after discharge is high among North Indian patients admitted with acute exacerbation. Poor functional status at discharge and advanced lung disease are predictive of excessive mortality. Advanced stage of lung disease is associated with frequent exacerbations.

P569
CURB-65 and mortality in pneumonic and non-pneumonic exacerbations of COPD
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Background: Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) requiring hospitalisation are often complicated by consolidation. In patients with pneumonia and AECOPD (pAECOPD) the CURB-65 prediction tool is widely used yet its utility in this population is uncertain.

Objective: To assess the effect of pneumonia on outcome, and the utility of CURB-65, in AECOPD.

Method: Patients hospitalised with AECOPD were recruited prospectively, with clinical data and CURB-65 collected on admission. Pneumonia was defined as the presence of new consolidation visible radiographically. Patients with pneumonia and AECOPD (pAECOPD) the CURB-65 prediction tool is widely used yet its utility in this population is uncertain.

Results: Of 920 patients recruited, 299 (32.5%) had complicating pneumonia. Patients with pAECOPD were significantly older (mean age 75.7 v. 71.8 years); more often male (50.8% v. 43.8%); and had slightly better preserved ventilatory function (FEV1 45.5 v. 42.9% predicted).

In-hospital mortality was higher in pAECOPD than in non-pneumonic exacerbation (npAECOPD) (20.1% versus 6.9%). The relationship of mortality with potential risk factors was analysed statistically by employing multiple logistic regression analysis, Kaplan-Meier survival analysis and Cox regression.

Results: Area under the ROC curve for CURB-65 against in-hospital mortality was 0.66 (95% CI 0.58-0.74) for pAECOPD and 0.72 (95% CI 0.63-0.81) for npAECOPD.

Conclusion: In pAE-COPD, risk of death is significantly greater than in npAE-COPD, and is higher than predicted by CURB-65. CURB-65 is a less good predictor of in-hospital mortality in pAE-COPD than previously reported in CAP, and other prediction tools may be required for this population.

P570
Anemia in COPD patients with an exacerbation
MCarmen Juarez Morales, Javier De Miguel Diaz, Teresa Gomez Garcia, Jorge Garcia Angulo, Jorge Chancafe Morgan, Gema Sanchez Mudoz, Luis Puente Maestu. Respiratory Medicine, Hospital General Gregorio Marlaon, Madrid, Spain

COPD typically shows poliglobulia secondary to hypoxemia. But, the opposite situation is also observed.

Aims: Quantify and classify the anemia in COPD patients with an exacerbation, describe clinical characteristics, factors which determine the anemia and the influence of the anemia in survival.

Methods: Observational prospective study of COPD patients with exacerbation. Demographic and anthropometric information as well as co morbidities and lung functional test is recorded. We measured survival after discharge and mortality risk factors.

Results: 106 were included (93 men). Average age was 71±6. BMI 25.7±5.6 kg/m2. FEV1 39±13%. 88.9% used to smoke or were smoking at present. Anemia prevalence was 37.7%. dyslipidemia (73.6%), high blood pressure (59.4%), heart failure (59.4%) and pulmonary hypertension (44.3%). Average Charlson index was 5.92±1.4 (87.9% ≥ 5), and the META index measured by bioelectric impedance was 22.3±7.8. 48.1% were taking more than 5 treatments. In logistic regression test factors that determined anemia were age, iron and creatinin levels (p<0.05) and the META index (p<0.01). Survival in patients with anemia at 39±4 months compared to 53±3 months in patients without anemia (p<0.001).

Mortality risk factors were FEV1, BMI and creatinin levels.

Conclusion: Anemia is frequent in COPD patients with exacerbation. Survival is clearly influenced by anemia. Age, iron levels, creatinin levels and META index influence the most.

P571
Our experience of procalcitonin assay in identifying bacterial COPD exacerbations
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Background: Procalcitonin (PCT) is a pre-hormone which is raised in bacterial infection.

Aim of study: To evaluate the benefit of measuring PCT level in recognising bacterial from non bacterial COPD exacerbations.

Method: We prospectively evaluated 24 COPD patients who were admitted with exacerbation. They had PCT, C-reactive protein (CRP), white blood cell (WBC) measurements and a chest radiograph (CXR). Use of antibiotics were recorded.

Results: 6 patients had CXR findings of consolidation and 5 of them had high PCT indicating bacterial infection. 1 patient had a moderately elevated PCT which could be due to early sampling. In 18 patients who had normal CXR findings, 3 had positive PCT and of these, 1 had high CRP and WBC indicating true bacterial infection. 1 had high CRP with normal WBC which could be due to atypical bacterial infection. 1 had normal CRP with high WBC which could be due to spurious low CRP result. 15 patients who had negative PCT, 7 had normal CRP and WBC indicating no bacterial infection. 2 of them had normal CRP but slightly raised WBC and we feel the raised WBC were due to preceding steroid treatment. 3 of them had raised CRP and normal WBC and 3 had both raised CRP and WBC. These may be due to bacterial infection, and the negative PCT represented early sampling. All patients had antibiotics on admission.
Conclusion: Many patients with COPD exacerbation are treated with antibiotics without bacterial infection. High PCT level indicates bacterial infection in these patients. The converse is also true but this should be used in conjunction with CRP and WBC. PCT level is associated with either raised CRP or WBC, a second late PCT level should be measured.

P572 Profile of patients hospitalized with COPD acute exacerbation in respiratory department in Tunisia

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In developing countries, Respiratory departments are facing new challenges with the huge increase in the number of patients hospitalized with COPD acute exacerbations with limits in ICU beds availability and delay in the management. The aim of this study is to outline the profile of patients with COPD exacerbation hospitalized in a respiratory department in Tunisia. Methods: A hand-made search of the main Spanish journals of COPD (Archivos de Bronconeumología, Revista Clínica Española and Medicina Clínica) and its references and a hand-made search from 2005 to 2010 of proceedings of annual congresses of European Respiratory Society, Spanish Society of Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; 3Department of Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; 4Department of Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; 5Department of Respiratory Medicine, University of Milan, Milano, Italy

Conclusion: Many patients with COPD exacerbation are treated with antibiotics without bacterial infection. High PCT level indicates bacterial infection in these patients. The converse is also true but this should be used in conjunction with CRP and WBC. PCT level is associated with either raised CRP or WBC, a second late PCT level should be measured.

P573 Anemia in COPD patients in Spain: A systematic review

Jesus Díez-Manglano1, José Barquero-Romero2. 1Internal Medicine, Hospital Royo Villanueva, Zaragoza, Spain; 2Internal Medicine, Hospital Tierra de Barros, Almendralaje, Badajoz, Spain

Objective: To determine the prevalence of anemia in COPD patients in Spain and the consequences of it.

Material and methods: We have conducted an electronic search in PubMed and Embase, a hand-made search of the main Spanish journals of COPD (Archivos de Bronconeumología, Revista Clínica Española and Medicina Clínica) and its references and a hand-made search from 2005 to 2010 of proceedings of annual congresses of European Respiratory Society, Spanish Society of Respiratory Pathology (SEPAR) and Spanish Society of Internal Medicine.

Results: We have obtained 11 studies, 2 journal papers and 9 congress abstracts. 7 studies were conducted in Internal Medicine departments, 3 in Pneumology departments and one in both. All studies used same criterion for COPD diagnose. Six studies defined anemia with WHO criteria and there was significant heterogeneity in exclusion criteria. The studies included 1669 patients, with a mean age of 74 years and 537 (32.2%) had anemia. Patients of Internal medicine departments were older (75.8 vs 70.7 years). There was no difference in prevalence by study department (Pneumology 50.2%, Internal Medicine 32.8%; p=0.32) but prevalence was lower with different of WHO diagnose criteria (24.5% vs 34.9%; p=0.0001). Anemia was not associated with readmission or mortality after three months in one study but was associated with readmission in the next year in one study and with one year-mortality in two studies. In one study anemia was associated with mortality during a median follow up of 531 days.

Conclusion: A third of Spanish patients with COPD had anemia. Anemia is associated with more long-term readmissions and mortality.

P574 Interleukin-6, but not pentraxin 3, predicts adverse clinical outcomes on short-term prognosis of patients with incipient heart failure

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Background: Bedside lung ultrasonography (BLU) is a technique performed and interpreted by the clinician who is in charge of the patient treatment. Even if recent studies show that BLU is beneficially useful in several diseases, the impact of this technique in clinical practice is still unknown. The primary aim of the present study was to analyze BLU indications in a respiratory medicine setting. The secondary aim was to describe the actual methodological application of BLU in the clinical practice.

Methods: Prospective observational analysis of consecutive BLU performed by pulmonologists at a University Hospital from April to May 2011. After each examination indication, methods and clinical consequences were recorded on a web-database.

Results: To date 88 exams on 88 patients (aged 42±34 years, mean±sd, 32 females, 32 pediatrics, 16 outpatients) were performed by 7 experienced operators. The quality of the examination was judged adequate in all patients. The most frequent indications were: lung consolidation (40%, of exams), pleural effusion (27%), guidance for thoracentesis (17%), acute respiratory failure (8%), and pulmonary edema (3%). The mean duration of the exam was 16±3 minutes. As a result of BLU, in only 8% of the cases chest X-ray or CT were needed. Bedside clinician reported that in 73% of the cases BLU had a significant clinical impact on patient management.

Conclusions: Our preliminary results suggest that lung ultrasonography performed by pulmonologist is a feasible procedure, widely used in clinical practice for many indications. Further studies are needed to evaluate the impact of BLU on patients management.

P575 Incidental abnormalities found on CT pulmonary angiograms performed for suspected acute pulmonary embolism

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A CT pulmonary angiogram (CTPA) is performed commonly in the investigation of suspected pulmonary embolism (PE). Other lung, mediastinal and pleural pathologies of clinical importance may be found incidentally, not suspected from the chest X-ray (CXR). We studied 500 sequential CTPA scans done for suspected PE in a community hospital to assess the nature and frequency of any pulmonary pathology first suggested by the CTPA, with particular reference to pneumonia not documented on the CXR. All CXR and scans were reviewed by a radiologist as well as the treating clinicians.

Retrospective observational study of CTPA for incidental pulmonary pathology

<table>
<thead>
<tr>
<th>CTPA</th>
<th>Pneumonia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE (+)</td>
<td>123 (24.6%)</td>
<td>37 (7.4%)</td>
</tr>
<tr>
<td>PE (-)</td>
<td>377 (75.4%)</td>
<td>83 (16.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>110 (22%)</td>
</tr>
</tbody>
</table>

Clinical diagnosis of the patient: PE. Vascular and parenchymal imaging

858
PE was found in 123 of 500 (24.6%) scans. 110 of 500 (22%) scans showed evidence of pneumonia. Out of these 110 scans, 55 had no evidence of pneumonia on the CR (of which 63% had been taken within 48 hours of the CTPA). Other pathologies were seen on 145 of 500 scans (29%).

Other pathologies seen on CTPA, (n=145):

- Pleural Effusion: 63 (43.45%)
- Lymphadenopathy: 15 (10.34%)
- Pulmonary nodules: 14 (9.65%)
- Metastatic lesions: 12 (8.37%)
- Others: 43 (29.7%)

Conclusion: This study is suggestive of a high incidence of pneumonia in patients scanned for suspected PE, half of whom had no consolidation in the initial CXR. This raises questions concerning the reliability of clinical decisions that rule out pneumonia when there is no consolidation on a CXR.

P577 Management of incidental lung parenchymal lesions found on CT pulmonary angiograms
Sharifa Sallehuddin, Said Isse, Peter Russell, Supriya Sundaram. General and Respiratory Medicine, Princess Alexander Hospital, Harlow, Essex, United Kingdom

Introduction: Incidental findings of lung parenchymal lesions are common. Many studies have described what these alternative diagnoses are, but few have looked at their management. We aim to investigate how these are managed in a UK district general hospital.

Methods: We retrospectively analysed all CT(PA) reports undertaken in 2008. We used Picture Archiving and Communication System (PACS) for CTPA reports. Pathweb for biopsy results and multidisciplinary team (MDT) database and patient case notes for the final clinical outcome.

Results: Of the 345 scans performed, 275 (80%) were reported as Low, 25 (7%) as Moderate and 40 (12%) as High probability of PE. 5 patients scans were not formally reported.

Conclusion: Management of incidental lung findings requires standardised follow-up and management plans in order to avoid delays.

P578 Diffuse pulmonary ossification (DPO) in the absence of interstitial fibrosis: CT findings and clinical correlates
James Gruden, Prasad Panse, Amy Trahan. Radiology, Mayo Clinic Arizona, Phoenix, AZ, United States

Introduction: Diffuse pulmonary ossification (DPO), or "dendriform" ossification, occurs in the setting of chronic lung diseases, particularly usual interstitial pneumonitis (UIP). It also can occur in association with severe emphysema or chronic lung infections. We have observed DPO on chest CT in the absence of chronic lung disease.

Objectives: We attempt to identify a cohort of individuals with CT findings of DPO in isolation in order to a) characterize the imaging appearance and b) assess potential clinical factors that may be associated with the development of DPO.

Methods: We performed an electronic search of chest CT reports between 2000-2011 at our institution for the word "dendriform". The CT studies were then reviewed by 3 thoracic imaging subspecialists who characterized the findings. Electronic medical records were reviewed for demographic and clinical information and follow-up data.

Results: 25 patients with CT findings of DPO in isolation were identified. DPO showed dense and soft tissue nodularity involving the peripheral interstitium (interlobular septae and subpleural space) especially in the posterior and lateral lower lungs with a costophrenic angle predominance. Patients were male, over age 70, and had few if any pulmonary symptoms. Smoking history was variable. Many had a history of or risk factors for aspiration. Serial scans, when available, showed progression of DPO over many years with minimal clinical change.

Conclusions: DPO can occur in isolation with a characteristic CT appearance, particularly in elderly men. It may indicate recurrent chronic aspiration in some cases. The findings progress over time with minimal clinical symptoms.

P579 Ventilation – Perfusion scan outcome when the chest radiograph is abnormal
Zahra Raisi Estabragh, Arun Lakanpal, Adiel Ashraf, Robert Hewson, Hassan Burhan. Respiratory Medicine, Royal Liverpool University Hospital, Liverpool, United Kingdom

Introduction: Guidelines recommend isotope lung scanning (V/Q) may be considered as first line investigation for suspected pulmonary embolism (PE) provided there are facilities on site and a chest radiograph (CRX) is normal. Occasionally, V/Q scans are performed in the presence of an abnormal CRX.

Aim: To study the diagnostic yield of V/Q scans in patients with suspected PE and an abnormal CRX.

Method: All patients who had a V/Q scan for suspected PE over a period of 12 months from February 2008 were included in the study. The CRX and V/Q scan reports were recorded.

Results: 1041 V/Q scans were performed at our institution with a preceding CRX. Of these, 345 CRXs were reported as abnormal.

- Other pathologies seen on CTPA (n=145):
  - Effusion 72
  - Consolidation 71
  - COPD 68
  - Atelectasis 48
  - Pulmonary Oedema 37
  - Nodules 8
  - Fibrosis 8

Of the 345 patients with an abnormal CRX that had a V/Q scan, 275 (80%) were reported as Low, 25 (7%) as Moderate and 40 (12%) as High probability of PE. 5 patients scans were not formally reported.

Conclusion: One third of the patients had a V/Q scan to investigate suspected PE had an abnormal CRX. Despite this, 275 (80%) of these patients had a low probability scan, 9 of these patients went on to have a CTPA and only 1 was positive for PE. A low probability V/Q scan may prevent unnecessary radiation exposure and adequately exclude PE, even in the presence of an abnormal CRX.

PS80 Ex vivo lung sonography: Morphological-ultrasound relationships
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The nature of lung ultrasound “artifacts” (B-lines, White Lung) has not yet been determined. We need to know what pathological structure and what physical mechanism create artifacts. We believe that lung ultrasonographic imaging is the acoustic behavior of ultrasonics crossing substrates of variable porosity or density. Each of 5 New Zealand white rabbit right lungs was sequentially inserted in cylindrical, rigid, hermetically sealed containers, with different volumes of 50 mL, 30 mL, 20 mL and 15 mL. Both lung and internal space of each container communicated with external air through a cork cap: the former through a cannula connected to trachea lumen and the latter through a tube connected to an aspiration system. Each system underwent negative pressure to get different known degrees of lung inflation. Densities were obtained for each lung at each level of inflation. Every lung was studied through ultrasonography and then sectioned and analyzed to correlate images with histological appearance.

In normal lung the variation of the pleural plane from specular reflector to generator of acoustic interference recognizes a mechanism which is related to values of tissue density. Artifacts described in lung ultrasonography as B-lines and White Lung appear in the normal lung through air dependent or weight dependent increases in density.

Conclusion: Ultrasound artifacts are density or porosity related. B-Lines and white lung (as in pathological conditions) can be reproduced in normal lungs that are deflated (i.e. denser or less porous) to levels of density which are not realizable under in vivo physiological conditions (< 0.45 g/mL). This mechanism is at the base of the genesis of artifacts also in the pathologic lung.
PS81 Agreement between clinical and HRCT diagnoses in the evaluation of patients with respiratory diseases
Kabali Nandakumar1, Ketaveseeram Vijayarath2, 1Respiratory Medicine, Queens Hospital, Burton-on-Trent, Staffordshire, United Kingdom; 2Respiratory Medicine, New Cross, Wolverhampton, United Kingdom

Aim: HRCT scans have been widely used in the diagnostic algorithm of respiratory diseases. In this study we aim to find out the agreement between clinical and HRCT diagnoses in such workup.

Methods: A retrospective study analysing 100 consecutive patients who had HRCT scans between July and September 2008. Data of scans and clinical information were obtained from electronic patients records.

Results: Total number of patients who had HRCT scan was 100. The average age patients was 65.3. Males constituted 61%. 76% of referrals were made by respiratory physician (RP), the rest from other specialties. The commonest presenting symptom was SOB (61%). Overall 54% of HRCT diagnosis correlated with clinical diagnosis. 76% request were made by RP of which 29% (38%) correlated with clinical diagnosis. A total of 38 patients had clinical sign on examination, 37 (97%) of these had HRCT findings consistent with clinical diagnosis but only 40 of the 62 patients (64%) with no clinical signs had clinical-angiographic correlation. 52 of the 56 patients (92%) who had prior chest X-ray abnormality which was later confirmed on a HRCT. The remaining 42 patients who had normal X-ray, only 20 (47%) had HRCT abnormality. The correlation increased to 96% when it was referred by a RP who had identified clinical signs and this further improved to a 100% when there was an associated CXR findings.

Conclusion: In this study only 54% of the patients had clinical-angiographic correlation. This correlation improved significantly to 100% when requested by RP who had identified prior clinical signs and chest X-ray abnormalities. Routine request for an HRCT scans are unsyndicated and should not be encouraged.

PS84 Abnormal chest radiographs preceding VQ scans: Does the type of abnormality matter?
Arun Lakanpal, Zahra Raissi Estabragh, Adeel Ashraf, Joseph Abbott, Robert Hewson, Hassan Burhan. Respiratory Medicine, Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom

Introduction: Abnormal chest radiographs (CXR) have been considered to affect the interpretation of Ventilation Perfusion scans (V/Q) for the investigation of suspected Pulmonary Embolism (PE). Recommendations suggest a V/Q scan only if a contemporaneous CXR is normal. Impact of individual CXR abnormalities on the outcome of V/Q scan has been fully explored.

Aim: To study the impact of individual CXR abnormalities suggestive of a range of cardiopulmonary diseases on V/Q scan results for the investigation of suspected PE.

Method: All V/Q scan and preceding CXR reports from February ’08-January ’09 at our 960 bed teaching hospital were included in the study.

Results: Data for a total of 1041 subjects who had a CXR prior to V/Q scan. The number of V/Q done on those with abnormal CXR findings was 345. The CXR abnormalities were classified as per the underlying cardiopulmonary pathology suggested by the report.

Discussion: Regardless of whether the CXR report preceding the V/Q scan was suggestive of infection, effusion, congestion or “COPD”, the proportion of low probability V/Q scans was high (71-95%). This proportion was particularly high at 95% (and with no high probability scans) in those with CXR suggestive of pulmonary oedema/congestion.

When used in the correct clinical context a V/Q scan can be used with a high degree of accuracy despite certain CXR abnormalities.

PS85 Limits of normality of quantitative thoracic CT analysis
Massimo Crescioni1, Davide Chiumello2, Eleonora Carlesso1, Elisabetta Gallazzi1, Antonella Marino1, Matteo Brioni1, Chiara Chiaruzzi1, Federica Ylenia Romano2, Daniela Februs1, Luciano Gattinoni1,2, 1Dipartimento di Anestesia, Rianimazione e Terapia del Dolore, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Milano, Italy

Introduction: Quantitative CT scan analysis has been widely studied in ARDS patients, while, data on healthy population are scanty. Reference values, however, would be of clinical relevance when assessing, i.e., the excess lung weight or edema, or whatever change in CT anatomy/physiology induced by disease.

Methods: We retrospectively included patients who underwent a spiral CT scan for clinical reasons and whose images were considered normal by radiologists. Lungs were outlined on each CT image with a dedicated software; lung weight, volume and tissue fraction were computed with a dedicated software.

Results: We enrolled 52 patients (25 males), age 65±12 years, height 1.67±0.09 m, BMI 26±4.8 kg/m². The table summarizes the main CT scan characteristics of patients, with CT taken at near total lung capacity. While the gas values are dependent on inflation, the lung weight is not. Therefore, of particular note the significant correlation between height and total lung CT scan characteristics

<table>
<thead>
<tr>
<th>Low probability V/Q</th>
<th>Intermediate probability V/Q</th>
<th>High probability V/Q</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CXR-Number (%)</td>
<td>590 (85%)</td>
<td>41 (6%)</td>
<td>65 (9%)</td>
</tr>
<tr>
<td>COPD-Number (%)</td>
<td>55 (8%)</td>
<td>4 (3%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Atelectasis-Number (%)</td>
<td>34 (7%)</td>
<td>5 (10%)</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Effusion-Number (%)</td>
<td>57 (79%)</td>
<td>9 (13%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Pulmonary Oedema-Number (%)</td>
<td>35 (95%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infection-Number (%)</td>
<td>57 (80%)</td>
<td>7 (10%)</td>
<td>7 (10%)</td>
</tr>
</tbody>
</table>

PS83 Early signs of hemoptysis, the advance CT approach
Tamará Milosavljević1, Aleksandar Ivićkovic2, 1Radiology, ZC Vranje, Vranje, Serbia; 2Center of Radiology, KC Nis, Nis, Serbia

Hemoptysis, the act of coughing up blood, is an important symptom since it frequently reflects serious underlying lung disease. If the hemoptysis is substansial, persistent, or recurrent then further evaluation is indicated, particularly since patients with chronic bronchitis related to smoking are at high risk for lung cancer. The aim of the study is to incorporate advance CT procedures in determining the right cause of hemoptysis and finding the right area of bleeding.

Material and methods: All patients were examined of 16 or 64 MDCT. We use standard lung procedure and all advanced MDCT methods, like 3D virtual bronchoscopy, nodule check, MDCT pulmonary angiography, very slow infusion injection of contrast agent, very fast bolus injection of contrast agent and wide specter of filters.

Results: We examined 1536 patients with coughing up blood and compared results on the most common causes with standard methods. Male patients were 917 and female 619, middle age of patients were 56.4 years. Our first aim was to find lung cancers in patients with recurrent hemoptysis where standard methods were insufficient. We found 18.76% more lung carcinomas in compare with standard procedures. Our second aim was to find right place of bleeding. In compare with standard methods we found the right place of bleeding in 21.54% more patients than with standard methods.

Conclusion: Improvements with advanced techniques are significant. Important is to notice that advanced techniques are not invasive and in any case danger to patients health.
Conclusions: Lung weight and volume are related to height in a healthy population.

82. From outside to inside: access to the pleura

PS86
A randomised controlled study to compare the efficacy of closed pleural biopsy and medical thoracoscopic pleural biopsy in undiagnosed exudative pleural effusion

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This study was to compare the efficacy of closed pleural biopsy with Abram’s needle and medical thoracoscopic pleural biopsy in the diagnosis of undiagnosed exudative pleural effusion in a tertiary care setting. It was a randomised controlled study during the period Nov 2008 - Oct 2010. All patients admitted with pleural effusion, underwent a clinical workup for pleural effusion during the period Nov 2008 - Oct 2010. Those patient’s with exudative pleural effusion without the establishment of a specific diagnosis were included in the study. The enrolled patients were then randomised into 2 groups. One group was subjected to medical thoracoscopic pleural biopsy and the other to closed pleural biopsy with Abram’s needle. Demographic, clinical & biochemical characteristics, diagnostic yield and the complications were of the two groups were compared.

58 patients were included in the study and they were divided into two groups of 29 patients each. The diagnostic yield was 86.2% in the medical thoracoscopic group as compared to 62.1% in closed pleural biopsy group. Complication rate was 10.3% in medical thoracoscopic group compared to 17.2% in closed pleural biopsy group. Hence the study concluded that medical thoracoscopic pleural biopsy had a better diagnostic yield with a lower complication rate as compared to closed pleural biopsy with Abram’s needle.

PS87
US guided thoracostomy true cut biopsy of peripheral pulmonary and mesothelial lesions

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1 Thoracic Surgery, 2Anesthesiology and Intensive Care, University Hospital of Pulmonary Diseases, Sofia, Bulgaria

Aim: The aim of the study is to evaluate the diagnostic value and the risk from US guided thoracostomy true cut needle biopsy (USG- TTBNB) for diagnosing peripheral thoracic lesions and its complications.

Materials and Methods: In a prospective study (from 1999 to 2007) we observed 753 patients with peripheral pulmonary and 273 patients with mediastinal lesions above 10 mm in diameter in 98% of patients peripheral thoracic lesions were assessed noninvasively. By all patients we performed USG-TTBNB (12-18G) under local anesthesia. The biopsy specimens were examined with light microscopy. Immunohistological analysis was carried out when needed.

Results: USG-TTBNB gave an adequate material to the morphological diagnosis in 698 (92.7%) of patients with peripheral thoracic lesions, PPV 98% and NPV 93.5%. We observed a few complications: 6 cases of pneumothorax (0.8%), by 2 patients it was necessary to set percutaneous tube drainage. USG-TTBNB of patients with mediastinal tumor masses yielded positive histopathological diagnosis in 250 (91.6%) of TCNB cases, PPV 98.1% and NPV 94.3%. There were no complications such as pneumothorax or serious bleeding.

Conclusion: US-guided thoracostomy cutting biopsy appears to be effective and a safe method in the patients with the US accessible thoracic lesions. This technique has a good accessibility, low cost, safety and high diagnostic accuracy compared to CT guided needle biopsy.

PS88
Ultrasound guided thoracostomy coaxial needle biopsy in chest lesions

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Aim: We examined diagnostic yield of ultrasound guided thoracostomy coaxial needle biopsy in chest lesions.

Material and methods: The 344 patients with ultrasonographically visible lesions of lung, mediastinum, pleura and chest wall were included in the study between August 2002 to January 2011. We performed TTNB with 18 gauge coaxial biopsy set. Five and more biopsies were performed for histologic examination. Immediately thereafter the lesion was aspirated with guide sheath connected to 20 ml syringe. Material retrieved by aspiration was proceeded to cytocoagulation and cell block was analyzed.

Results: A total of 344 patients were included from August 2002 to January 2011. Median age was 63.7 years (range 25-84 years), 20.7% were male. The majority of cases were lung lesions extending to the pleura (n=311, 90.4%), followed by pleural lesions (n=21, 6.1%), mediastinal lesions (n=8, 2.3%) and chest wall lesions (n=4, 1.2%). At the time of biopsy, a chest radiograph was available in all patients. Minimum lesion size was 3 cm.

Final diagnosis was established in 284 patients (82.56%), 60 patients (17.44%) were diagnosed by other means or were undiagnosed. 221 (77.82%) lesions were malignant, 63 (22.18%) were benign. The diagnostic yield TTBNB was 82.56%.

Adverse events were pneumothorax in 22 patients (6.4%) and in 8 of these, a chest drain was required (36.36%). Mild hemothorax (n=18, 5.2%), post procedural pain requiring medication (n=8, 2.3%), vagovascular reaction (n=6, 1.7%) were minor events.

Conclusions: Coaxial needle biopsy set technique is safe method with excellent diagnostic accuracy. This technique has advantage that several samples may be taken without having to repeatedly penetrate the pleura.
the operator, very low rate of complications and short acquisition time of the pleural space. Our new technique, real time echo guided costophrenic cannulation with Veress needle, allows to broaden the field of applications of thoracoscopy and might be used in patients who cannot maintain orthostatic position.

PS91 Medical thorascopic lung biopsy obtained by stapler device: A new trick in old ground?
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Introduction: Recent advances in minimally invasive techniques and instrumentation have expanded the role of medical thoracoscopy. The introduction of an endoscopic stapling device has encouraged thorascopuc lung biopsy.

Aims and objectives: Evaluation of the quality of biopsy, the diagnostic efficacy and yield in high risk patients (pts) who underwent medical thorascopic lung biopsy (MTLB) for the evaluation of peripheral mass or diffuse interstitial lung disease using a stapler device under regional anesthesia and neuroleptic analgesia.

Materials and methods: During 2002-2011, 30 high risk pts (75% severe respiratory failure, 40% renal failure, 33% ischemic stroke) underwent MTLB. Biopsy samples were obtained by a stapler device. Midazolam and fentanyl were used for anesthesia and intercostal block was performed in all patients with ropivacain.

Results: Pts were 18 males and 12 females (mean age 68.9 years, range 28-75 years). Mean duration of the procedure was 30 min (15-35 min). No intra-/post-operative deaths nor major complications were recorded. Successful analysis was obtained in all pts. Biopsy specimens from the stapler device had mean dimensions: 3.2x1.7x0.9 cm (mean volume: 3.61 ccm). All lung biopsies were conclusive and diagnostic. Malignancy was diagnosed in 17/30 pts and nonmalignant conditions in 13/30 (43% interstitial lung diseases, 50% interstitial pneumo-nia, 7% infarct). No complications were recorded.

Conclusions: Stapler tissue specimens received by MTLB have a high diagnostic accuracy in pts with peripheral tumours and diffuse interstitial lung disease. MTLB by stapler device is a pioneer method ensuring superior quality of biopsy and can be applied in high risk pts without complications.

PS92 Alternate drain of thoracic cavity by Seldinger technique in a tertiary healthcare setting
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Introduction: Chest drain insertion is often required in the clinical practice. Large bore catheters are difficult to insert and may be associated with adverse complications. Seldinger drainage kit has been introduced to minimize the complications associated with conventional tube drainage.

Aims and objectives: To share our experience in 850 patients who were inserted a portex Seldinger drainage kit (SDK) 12 F during the period 01/2001-02/2011.

Materials and methods: Details of all SDK insertions were retrospectively collected by the respiratory team. This observational study looked at the indications, success, complications and patient outcome.

Results: Eight hundred and fifty pts (mean age: 65.7 years, range: 18-92) were inserted an SDK due to pleural effusion (500 patients), pneumothorax (250 patients), traumatic hemothorax (100 patients). Successful drainage was obtained in all patient without any complications at insertion except for 1 case of hemothorax in a patient receiving anticoagulant therapy. Thirty patients had a malignant pleural effusion and underwent pleurodesis with bleomycin or novodrin. In pneumothorax, the mean stay of drain was 3 days (range 2-15 days).

Conclusions: SDK is a minimal invasive and effective alternate method for pleural space drainage with minor complications. SDK training should be regularly applied in young doctors to ensure the quality and efficacy of performance.

PS93 Thorascopic findings of undeterminate eosinophilic pleural effusion
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Background: An etiologic diagnosis cannot be established in 14% of eosinophilic pleural effusions, and these cases are referred as idiopathic. Yet, thorascoscopic diagnostic approach in this entity has never been studied. The aim of our study is to assess thorascoscopic findings in patients with undeterminate eosinophilic pleural effusion.

Methods: We studied all patients with undeterminate eosinophilic pleural effusion during the last 4 years among 168 patients who underwent medical thorascopy for diagnosis. Pleural effusion was considered eosinophilic when contained more than 10% of eosinophils. Effusion was classified as idiopathic if no etiology could be assigned during evaluation. All patients were followed at 1, 3, 6, 12 months.

Results: Patients with undiagnosed eosinophilic effusion were 8 (4.5%). Pleural eosinophilic count ranged from 10% to 99%. Macroscopical examination of the pleura during medical thorascopy demonstrated diffuse thickening, associating to inflammation in six patients and scattered nodules in two. Microscopical examination of pleural biopsies evidenced non-specific inflammation with eosinophilic predominance in all of our patients. Specific diagnosis was not identified in all cases. None of the patients received any specific treatment during the follow-up period. No relapse of pleural effusion was recorded.

Conclusion: Idiopathic eosinophilic pleural effusions are associated with nonspecific eosinophilic inflammation of the pleura. They usually follow a benign course with a resolution within a year without the administration of any specific therapy and a conservative approach with observational follow up is recommended.
P596

Medical thoracoscopy – A district general hospital experience

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The 2010 British Thoracic Society (BTS) guideline recommends the use of Medical Thoracoscopy (MT) in the management algorithm for malignant pleural effusion [1]. Despite this MT is not readily available outside of tertiary centres in the United Kingdom [1]. An internal audit in 2010 showed the burden of pleural effusions at Barnsley Hospital (BH) over an 18 month period led to 1195 medical admissions; 226 (18.9%) were malignant effusions.

The process diagnostic for exudative pleural effusions has altered recently in BH to include semi-rigid MT.

Method: A retrospective analysis of computed tomography (CT) reports, histology and length of stay (LOS) for all individuals who underwent diagnostic MT (dMT) was performed.

Results: 44 MTs have been done to date. 32 were diagnostic and 12 therapeutic. Diagnostic MT results are as follows:

Adenocarcinoma 10, Melanoma 2, Breast Carcinoma 3, Ovarian Carcinoma 1, Tuberculosis (TB) 2, Inflammatory Tissue 14.

CT reports prior to dMT revealed a low suspicion of malignancy in 18 and a high suspicion of malignancy in 14. dMT histology confirmed malignancy in 14 patients within the high suspicion group. Within the low suspicion group dMT histology confirmed 2 cases of lung cancer, 2 cases of TB and no evidence of malignancy in 14.

Average LOS after dMT was 3.7 days (range 1-11). The average LOS prior to the introduction of MT was 7.3 days (range 1-59).

Conclusion: MT is cost-effective through reducing LOS and referral rates to tertiary centres. As this study has highlighted a potential missed or delayed diagnosis in 12.5% of cases. Patient experience is improved by facilitating a timely patient journey within their local hospital.

Reference: [1] BTS Pleural Disease Guidelines 2010

P597

Pigtail catheter drainage – When to use it

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Chest drainage for patients (pts) with pneumothorax or various etiology pleural effusions is a method of choice. In some circumstances specialists use a tip with a curled drain-pigtail catheter (PC).

Aim: To share our experience with pigtail catheter drainage.

Method: 106 pts were drained in 2010. A pigtail catheter was used on 17 pts (16%). Pts 14 or 16 CH were preferred. The site of insertion was determined using a sonography examination. PC with a trocar was inserted into the skin incision. After insertion of the drain the end of the catheter was twisted by pulling back the synthetic fibres and then fixed. The luer end of drain was connected to a Heimlich valve and then to a urine bag. When production of PE was < 100 ml/24 hours, the drain was removed.

Results: Out of 17 pts, 13 were M, mean age 60 (22-85 yrs), 4 were F, mean age 53.5 (42-69 yrs). The most frequent reason was encapsulated empyema in 8 pts, malignant effusion in 6 pts and TB, hemothorax and non- specific pleuritis in the remaining 3 pts. Pleurodesis was successful in 2 pts died during drainage (both from malignant effusion). The median duration of the chest drainage was 9 days (4-21 days).

Conclusions: The main advantage of using a PC was that the small space in encapsulated empyema is too small for using a conventional drain or when there is a suspicion of septated PE. The disadvantage of pigtail drainage: 1.twisted end impedes the re-expansion of the drained cavity, 2. the system with a trocar is sharp and so careful consideration should be given to the indications (avoid drainage of lung abscess), 3. removing the drains is more painful, 4. is more expensive than a normal catheter.

P598

Prognostic factors in patients with malignant pleural effusion undergoing thoracoscopy

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Background: Survival of patients with malignant pleural effusion is considered generally poor. These patients are likely to undergo thoracoscopy for diagnosis and treatment of their disease. Factors affecting survival are important to define to decide whether patients should undergo interventional procedures. The aim of our study was to evaluate prognostic factors of patients with malignant pleural effusion undergoing thoracoscopy.

Methods: Patients with malignant origin proven by thoracoscopy, have been studied prospectively to determine prognostic factors. Survival time was defined as the time interval from thoracoscopy to death or last follow-up. A regression model was used to assess significant prognostic factors.

Results: 90 patients with histological diagnosis of malignant pleural effusion after thoracoscopy, were included. Diagnosis was lung carcinoma 43%, breast carcinoma 23.6%, mesothelioma 12.9%, genito-urinary carcinoma 7.1%, GI 4.8%, other 5.1%, unknown primary 3.5%. The median overall survival time was 11 months ranging from 1 to 55. The Cox analysis showed that histology of the primary tumour (p=0.019), ps (p<0.001), gender (p=0.01), WBC (p=0.01) and neutrophils/lymphocytes ratio (p=0.018) were prognostic factors for survival. In the multivariate analysis, histology was an independent factor (p=0.002), performance status (p<0.001) and WBC (p=0.01).

Conclusion: Performance status, histology of the primary tumour, and WBC are factors of survival in patients undergoing thoracoscopy for malignant pleural effusion. The prospective identification of patients meeting these criteria may help physicians select patients for interventional procedures.

P599

Clinical utility of thoracoscopy under local anaesthesia in undiagnosed pleural effusion

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Introduction: More than twenty percent of pleural effusions remain without an established aetiology after evaluation with pleurocentesis and closed pleural biopsy. Thoracoscopy under local anaesthesia greatly increases the diagnostic yield for undiagnosed pleural effusion and is taken as the gold standard diagnostic procedure.

Aims and objectives: To assess the utility and safety of thoracoscopy under local anaesthesia in the evaluation of undiagnosed pleural effusion.

Methods: This is a retrospective study of all patients with undiagnosed pleural effusion who underwent thoracoscopy under local anaesthesia between January 2008 and December 2010 in a tertiary care hospital.

Results: 52 patients (33 males and 19 females) underwent the above procedure during the period of study. Mean age of patients was 41.2 years (range: 19-78 years). Histopathological examination of thorascopic pleural biopsy revealed: malignancy in 34 (65.4%) cases, benign tumour (fibroma) in one (1.9%), tuberculosis in 14 (26.9%), empyema in two (3.8%), and nonspecific inflammation in one (1.9%) case. Diagnostic efficacy of medical thoracoscopy was found to be 98.1% (51/52).

Conclusions: Medical thoracoscopy is a safe, well tolerated and effective procedure.

P600

Low dose vs high dose talc pleurodesis for malignant pleural effusion

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Introduction: Role of talc in pleurodesis for recurrent pleural effusion is very well defined. In developing countries like India, talc is still the cheaper and commonly used pleurodesis agent. However, it has been known to be associated with a lot of morbidity including ARDS. Common morbidities include fever, chest pain, nausea and vomiting. The aim of this study was to see the effectiveness of low dose talc pleurodesis, and to evaluate if low dose talc is associated with lesser complications.

Method: 24 adult patients of malignant pleural effusion were included in the study. Patients were divided in two groups. In group A (n=10), 5 gm of talc was used while in group B (n=14), pleurodesis was done with 10 gm of talc. Equal amount of xylcocaine and normal saline was used in both the groups. Standard method for pleurodesis was followed. Close observation was done for next 48 hours, and after that patients were followed every week till 6 weeks.

Results: Immediate complication in terms of fever, chest pain and nausea was seen in 40% (n=4) patients of group A where 5 gm of talc was used. When these patients were followed up for next 6 weeks, 30% (n=3) of patients showed recurrence of effusion, and required repeated thoracocentesis. In group B, 64% (n=9) patients developed immediate complications in terms of high grade fever, and vomiting. However, in group B also, 36% (n=5) patients showed recurrence of pleural effusion and required repeated thoracocentesis. ARDS was not seen in either group.

Conclusion: Talc pleurodesis with lower dose of 5 gm is associated with lesser number of complications and is equally effective as with 10 gm of talc.
P601 Feasibility and complications of relatan catheter insertion after pleural biopsy as a novel method for pleural fluid drainage
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Backgrounds: Respiratory failure due to massive pleural effusion is usually treated with drainage via a chest tube.

Objectives: To investigate feasibility and complications of Nelaton catheter insertion after pleural biopsy as a novel method for pleural fluid drainage.

Methods: After pleural biopsy, a Nelaton catheter No.18 was inserted in the pleural space guided by Abram biopsy needle, after drainage control chest radiography was performed. Complications and daily examination results were recorded.

Results: 46 catheter insertions were performed on 41 patients (22 men, 19 women). Among these patients, pleural biopsy was indicated in 40 (78%) of them. Four patients underwent pleurdesis because of malignant pleural effusion due to breast cancer. Successful fluid drainage after catheter insertion was observed in all 46 cases. Dyspnea was significantly decreased after catheter insertion in all patients. Mean drainage duration was 5.3 days. In 42 (91.3%) patients complete lung expansion was observed. Incomplete lung expansion was observed in 4 patients (2 patients due to trapped lung, and 2 patients due to loculated pleural effusion). Catheter obstruction was occurred in 12 patients which was resolved after Salin wash out in 11 cases.

Conclusion: Nelaton catheter insertion after pleural biopsy is a novel, cost effective, simple and tolerable methods with low morbidity for drainage of pleural effusion in symptomatic patients undergo pleural biopsy. Common complication of this method is catheter obstruction which could easily be resolved with Salin wash out.

P602 Pleuroscopy with an autoclavable semi rigid thoracoscope
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Aim: Describe our experience with a endoscope similar in design to commonly used bronchoscope. This pleuroscope interfaces with processors and light sources employed for flexible bronchoscopy and, therefore, are available in most endoscopy units.

Method: Pleuroscopies were performed under local anaesthesia with conscious sedation. by a Respiratory Physician in a endoscopic suit. A single puncture technique and pleuroscope Olympus LTF-160 was used.

Results: 31 pleuroscopies undertaken over a 14-month period. From the 31 patients, 22 were men, and 9 women, mean age of 68.6. Four patients have bilateral pleural effusion. 17 procedures were performed on the right pleural space, and 14 on the left. The indication in 22 procedures was for diagnostic of a pleural effusion, in the other 9 procedures, the indication was pleurodesis in patients with previous diagnostic of malignancy. Pleural biopsy were obtained in the 22 patients and a histologic diagnosis of malignancy was made in 10 (3 mesothelioma and 7 metastasis of carcinoma) six patients have non specific pleuritis and 2 patient has necrotizing granulomas. In 3 patients with previous diagnostic of malignancy (esophagus and 2 bronchial carcinoma), metastatic pleuraly were ruled out. In 18 patients, pleurodesis with talc poudrage was performed. There were minor complications in 3 patients (1 subcutaneous emphysema, 1 infection of point of needle and 1 traumatic in the 6 hours after the procedure).

Conclusion: The Pleuroscopy with autoclavable semi rigid thoracoscope is a safe and useful technique in the diagnosis and management of pleural diseases. The semirigid pleuroscope must increase the performance of pulmonologists in the diagnosis and management of pleural disease.

P603 Retrospective evaluation of effectiveness and safety of local anesthetic thoracoscopy compared with blind chest drain pleurodesis
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Aim: To retrospectively evaluate effectiveness and safety of local anesthetic medical thoracoscopy and talc poudrage (TP) compared with chest drain and talc slurry pleurodesis (TS) in a district general hospital (DGH) without onsite thoracic surgery backup.

Methods: Data was collected between July 2007 and February 2010 using multidisciplinary team minutes and pharmacy records. All patients with malignant effusions who had treatment and had follow up were included. Patients with no diagnosis or follow up and those who did not have TS/TP were excluded.

Results: 104 patients were identified. 12 patients were excluded due to inclusion and exclusion criteria. Mean age in TS vs. TP was 71.5/7.14 years. Pleurodesis success rate in TS vs. TP was 22.8/7.5%. In the TS group, 75% of patients with a successful pleurodesis were receiving chemotherapy. The average time from pleurodesis to death in TS vs. TP was 201/359.6 days. Of the 14 failures in the TS group 64.2% (9/14) died within 6 months and 28.6% (4/14) had mesothelioma. In the TP group 79.1% (19/24) were alive at 6 months and 66.6% (2/3) of the failures had mesothelioma. Two of the 3 patients with failed TP were recruited in an ongoing trial involving a drug therapy and pleurodesis success rates. Mean follow up, TS vs. TP was 67.7/208.3 days. No serious complications were documented in either group.

Conclusion: To the best of our knowledge this is the first local anaesthetic thoracoscopy data comparing with TS in a DGH setting. The TP group has a success rate on par with published data. Based on this data we may conclude that local anaesthetic TP is effective and safe in patients with reasonable performance status.

P604 Safer intercostal drain (ICD) insertions
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Introduction: Intercostal chest drain (ICD) insertion carries a small but significant risk to patients when not performed properly. We re-audited the practice of ICD insertion in our hospital following several implementations since a previous audit in 2007-08. These implementations include drain insertion in specialised areas i.e. respiratory unit treatment room, strict sterility, ultrasound guidance, insertion sticker check list and nursing care plan.

Results: There were a total of 31 patients (15 males) in the bi monthly audit from March '09 to January '10. Majority of the ICD insertions (87%) were performed in the respiratory unit and ultrasound guidance was documented in only 41.9%. ICD stickers were used in 83.9% and nursing care plan in 77.4%. Excluding the adverse event “pain”, complications rates in our hospital decreased from 39% to 12.9% in 2009-10 (Table 1). This is comparable with the complication rates of other centres (11-37%) [1]. Adverse events were significantly higher when drains were inserted outside a respiratory unit (p=0.007). Surprisingly, we found no statistical differences between complication rates and the use of ultrasound guidance, sticker check list; or nursing care plan.

Conclusion: ICD insertion is advised to be performed in a specialised unit by staff with relevant competencies under adequate supervision.

References:

P605 A new electronic device for intrapleural pressure measurement – A presentation of use in a patient prepared for thoracoscopy
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Background: Measurement of intrapleural pressure is useful during various pleural procedures. However, the availability of electronic pleural manometers is limited.

Objectives: We aimed to 1) construct an electronic pleural manometer, 2) assess the accuracy of the measurements done with a new device, 3) perform an initial evaluation of the device during thoracoscet.

Methods: A vascular pressure transducer was used to transform hydrostatic pressure into an electronic signal. Reliability of the measurements was evaluated in a laboratory setting by comparing the results with those measured by a water manometer. Functionality of the device was assessed during thoracoscopic and artificial pneumothorax creation before medical thoracoscopy.

Results: We built a small device, which can precisely measure intrapleural pressure. The measurement results showed a very high agreement with those registered with a water manometer (no.999; p=0.001). The initial evaluation of the electronic manometer during pleural fluid removal and pneumothorax creation showed the mean initial intrapleural pressure 3.85 cmH2O which decreased steadily to -8.98 cmH2O after the removal of 1600 ml of pleural fluid and increased up to -1.29 cmH2O after insertion of 1000 ml of air. The procedure was safe, the only symptom recorded was cough which appeared after the withdrawal of 900 ml of pleural fluid (intrapleural pressure -1.96 cmH2O).

Conclusion: Our electronic pleural manometer can precisely measure intrapleural pressure during pleural fluid removal and pneumothorax creation. The procedure of pleural pressure monitoring during thoracoscet is easy to perform and safe.

Table 1. Complications rates excluding pain

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocked drain</td>
<td>2</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
</tr>
<tr>
<td>Surgical emphysema</td>
<td>1</td>
</tr>
<tr>
<td>No complications</td>
<td>27</td>
</tr>
</tbody>
</table>

SUNDAY, SEPTEMBER 25TH 2011
83. To stent or not to stent: interventional bronchoscopy

P606 Interventional management versus standard treatment for inoperable malignant airway obstruction

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Although endoscopic management of malignant central airway obstruction (mCAO) is well established, not enough survival and quality of life (QoL) data exist comparing it with sole chemo-radiotherapy.

We prospectively studied patients referred to our unit for mCAO using the EORTC QoL questionnaire, at one day before, 1 week after and every following month.

40 patients (31 males) aged 66.2±12.3 (mean±sd) with either non-small cell lung cancer (n=35) or metastatic malignancies, were included. 31 patients (intervention group) underwent extensive interventional bronchoscopic management as indicated, whereas 9 declined endoscopic treatment (control group).

Patients of the two groups did not statistically differ in age, comorbidities, type of malignancy and level of obstruction. Overall follow up time was 6.6±6.2 (range 1-26) months. 13 patients are still alive followed for 6.6±7.6 months (range 1-26). QoL and dyspnea significantly improved in all patients of the intervention group up to 1 month after the procedure (p<0.05). Improvement was greater in those initially presenting with atelectasis and tracheal obstruction. Dyspnea remained significantly improved in treated patients up to the 6th month. For those surviving over the 9th month (n=11) and those surviving over the 12th month (n=6), QoL and dyspnea did not significantly deteriorate. In all time points, control patients had worse QoL and dyspnea (p<0.05). Mean survival time for intervention and control group were 20.7±4.23.57 and 6.3±4.7 months respectively.

Interventional bronchoscopy may achieve prolonged survival, significant and sustained QoL and dyspnea improvement, in patients with airway obstructing malignancies.

P607 Bronchoscopic assessment of airway invasion by esophageal cancer: A retrospective study

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Background: Fiberoptic bronchoscopy (FOB) is frequently used to evaluate possible invasion of the tracheobronchial tree by esophageal cancer.

Objective: To evaluate the diagnostic utility of FOB for the assessment of airway involvement by esophageal carcinoma and its resectability.

Material and Methods: Retrospective study of bronchoscopies in patients with potentially operable esophageal carcinoma, correlating its findings with other staging modalities, in the last 6 years.

Results: We included 40 patients, 87.5% male, mean age 63.4±13.2 years. Respiratory symptoms appeared in 15% of cases, all of them with endoscopic abnormalities.

In 16 (40%) patients, FOB revealed: extrinsic compression in 12 (30%) and endoluminal endoscopy in 4 (10%) cases. These features were more frequent at the left main bronchus (n=5) and middle third of the trachea (n=4). Comparing CT with FOB, we found that observed or suspected invasion of the trachea on CT (21 patients), was only confirmed by FOB in 4 cases (19%). In 3 patients with endoscopic abnormalities, CT revealed no invasion of the bronchial tree. In cases of suspected airway involvement (n=8) by endobronchial ultrasound (EUS), 3 had wall protrusion without evidence of mucosa’s infiltration. The overall accuracy of FOB with multiple brush cytology and bronchial biopsy in confirming or excluding airway invasion was 95%. Normal endoscopic appearance had a negative predictive value of 100%.

In 3 patients FOB was the decisive staging procedure, excluding surgical treatment.

Conclusion: Bronchoscopy with biopsy and brush cytology is a very accurate procedure in assessing potential airway invasion by esophageal cancer. CT and EUS findings alone are not reliable.

P608 Postintubation tracheal stenosis – A 15 year experience

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Background: Postintubation injury, with or without tracheostomy, is the most common cause of benign tracheal stenosis (TS).

P609 Endoscopic management of idiopathic tracheal stenosis

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Background: Idiopathic tracheal stenosis (ITS) is a rare condition. A therapeutic option is endoscopic management, but long term results are not established. The aim of this retrospective multicenter study was to analyze long-term outcome after endoscopic management of ITS.

Methods: Patients endoscopically treated for ITS were included in 9 institutions involved in interventional bronchoscopy. A standard form was used to report patients and stenosis characteristics and long term outcome after endoscopic management.

Results: Twenty-three patients, 96% women, age: 45±16 years, were endoscopically treated for ITS. Time between first symptoms and diagnosis was 19±18 months. Bronchoscopy showed a web-like (61%) or complex (39%) stenosis, located in the upper part of the trachea mainly in the cricoid area. Endoscopic treatment included mechanical dilation only (52%) or associated with laser or electrocautery dilatation (30%) and stent placement (18%). All procedures were efficient with no morbidity or mortality reported. The follow-up after endoscopic management was 41±34 months. ITS recurrence occurred in 30% at 6 months, 59% at 2 years and 87% at 5 years with a delay of 14±16 months. The treatment of recurrence (n=13) included endoscopic management in 12 cases.

Conclusion: Endoscopic management of ITS provides a safe and efficient therapeutic option but late recurrences are frequent and requires long term follow-up.

P610 Airway measurements in tracheobronchial stenosis using endobronchial ultrasonography during stenting

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Purpose: To assess airway measurements, endobronchial ultrasonography (EBUS) and multi-detector low computed tomography (MDCT) images are compared in patients with tracheal stenosis.

Methods: Airway stenting was performed on 31 patients, 25 malignant and 6 benign. EBUS and MDCT images were compared before intervention and on the narrowing airway at 212 sites. Of these, 130 sites were considered normal and 82 abnormal. For malignant stenosis, airway measurements were taken at 160 sites including 112 normal and 48 abnormal. For benign stenosis, airway measurements were taken at 52 sites including 18 normal and 34 abnormal. This technique enables the EBUS probe to measure the distal end to proximal end of the stenosis whereby the inflated balloon size changes according to the degree of stenosis.

Results: The diameter and length of stenotic sites measured by EBUS and MDCT were near equal in all patients. Significant correlation was seen at all 212 sites.
Our experience revealed that topical application of MMC can be useful, the mean time since granulation and symptoms improvement is 17.3 months, and tissue in 43%, moderate in 29% and relapsing in 29%. At this moment, after MMC patients. Mean MMC sessions 2.7, with good and lasting decrease in granulation healing and scarring. Its topical application, as an adjuvant treatment in endoscopic management of stenosis, has showed good results.

Aim: Evaluate the results of MMC application by Rigid Bronchoscopy (RB) in PITS.

Methods: Selected patients with PITS, in whom MMC was applied it was used in a concentration of 0.4 mg/ml, applied with a cotton stiletto around granulation tissue, for 2-3 minutes, after RB dilatation or laser. Re-evaluation and MMC application was done according to evolution. Patients were evaluated for kind, location and stenosis size (%), treatment procedures and results with adjuvant MMC application.

Results: 7 patients, 71.4% women, mean age 55.4 years. Mean initial stenosis diameter 50% of airway lumen, mostly located 1-3 cm below vocal cords, with 1-2 tracheal rings involvement. Stenosis RIB dilatation, laser and MMC were made in all patients. Mean MMC sessions 2.7, with good and lasting decrease in granulation tissue in 43%, moderate in 29% and relapsing in 29%. At this moment, after MMC use, the mean time since granulation and symptoms improvement is 17.3 months, and mean final airway diameter 70% of the lumen.

Conclusions: Our experience revealed that topical application of MMC can be beneficial in the modulation of wound healing and in the decreasing scar formation in the treatment of airway stenosis. Further research and randomized prospective clinical trials are needed to determine the most effective concentration, time and frequency of exposure to MMC.

The management of post-intubation/traechostomy stenosis with silicone stent
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Benign tracheal stenosis in adult patients may occur as a complication of intubation, tracheostomy or surgical procedure. Silicone airway stenting has opened up a new way to treat patients with post-intubation stenosis. We investigated the clinical efficacy by a review of patients with post-intubation stenosis who underwent consecutive Natural silicone stent. Between January 2005 and December 2007, 19 patients underwent ballooning, ablation using electro-surgical unit, or bougienage by rigid bronchoscopy, followed by placement of the Natural silicone stent. All patients reported subjective symptoms of symptoms immediately after stent placement. Spirometry data was collected at baseline, 3 months, and 24 months. The baseline and follow-up spirometry data was available in 11 patient. The baseline median FEV1% predicted was 40% (range, 22% to 62%). Follow-up spirometry showed 37% improvement (range, 19% to 74%) at 3 month later, and 41% improvement (range, 21% to 77%) at 24 month later.

The Natural stent were removed successfully in 10 patients (52.6%) after median of 16months. Other 5 patients (26.3%) were required re-stenting, and 4 patients died due to acute pulmonary edema with ESRD, myocardial infarction, intracranial hemorrhage. The Natural silicone stent proved to be effective and feasible therapeutic modality in improving quality of life with relief of dyspnea.

Post-intubation tracheal stenosis represents a severe complication in patients with hypercapnic respiratory failure due to COPD. We present a series of iatrogenic tracheal stenoses in COPD patients addressed to the Bronchiology Department during 5 years. There were 13 patients (10 males, 46% over 60 years old), COPD stage III-IV GOLD, who suffered a severe exacerbation that required oro-tracheal intubation; 8 needed tracheotomy Tracheal stenoses developed after a mean period of 24 days (7-42) and were clinically significant. Bronchoscopy revealed tracheal stenosis with diameter less than 5 mm. 8 were located in proximal trachea and 5 in medial trachea, with length more than 2 cm in 7 cases and less than 2 cm in other 6. Initially, all were treated with interventional bronchoscopy (dilatation, granuloma resection) but the results were unstable in time, requiring other methods: prosthetics (8 cases) or surgery (5 cases). In the patients treated by prostheses, the stent was removed in 3 cases after 1.5-2.5 years, the rest remained chronic carriers of prostheses. The patients treated by surgery had significant complications: 1 death by mediastitis, 3 stenosis relapse on the anastomosis line (finally resolved with interventional bronchoscopy). Only one case was successfully solved after surgery. In conclusion, interventional bronchoscopy had a higher success rate (37%) than surgical therapy (20%), also solving the cases complicated post-surgery with reocurrence of stenosis. While for different etiologies of tracheal stenosis, surgical resection is the first choice of treatment, in patients suffering from COPD, interventional bronchoscopy remains the only way to solve it.

Endobronchial stent therapy is an accepted method for the treatment of endobronchial stenosis. It is limited by a loss of physiologic surface and, thus, mucus retention. We developed a novel concept for a viable endobronchial stent (fig. 1 A). The concept is based on the combination of stent technologies with the principles of tissue engineering. The RespStent provides (1) a functional respiratory epithelium on the luminal side, which allows the maintenance of the mucociliary function in the stented area and hereby will help to reduce complications of mucus retention, (2) embedded micro- or nanostructures, enabling the sus-
Incidence of bacterial colonization in patients with tracheobronchial stents
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Objective: To describe the prevalence and incidence of potentially pathogenic microorganisms (PPM) colonizing the airways of patients with tracheobronchial stents.

Methods: We collected bronchial washings from patients treated endoscopically for neoplastic or benign tracheobronchial stenosis.

Results: We retrospectively studied 39 patients during a median of 128 days (12-448), 12 (31%) COPD with FEV1% of 58%, benign disease 5 (13%) and malignant 44 (23%).

Conclusions: The main colonizing PPM are P. aeruginosa (158,4%) and S. aureus (9,2%) with a prevalence of 87,5% after 12 months. In 37 pts withopleural carcinoma, 8 pts with bronchial/tracheal cancer, 8 pts with other tumours, 9 cases with tracheostomy or tracheal intubation, 8 traumatic cases and 5 consequences with endoscopic therapy (laser, esophageal stent, bronchoscopic apy).

P618 Tracheo-esophageal phistula: The role of bronchology
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Tracheo-esophageal phistula (TEP) is a complex condition with different etiology and prognosis. Present study evaluates a series of patients (pts) with TEP according to etiology, complications, survival and endobronchial treatment. Among 50 pts there were 41 (82%) men and 9 (18%) women, mean age was 62.2 years.

Tracheobronchoscopy was the diagnostic method of choice, other methods were anamnesis, chest X ray, 3Dimensional CT and esophagogyscopy. Malignant disease was the cause of TEP in 33 (66%) pts, benign disease in 17 (34%) pts. There were 17 pts with esophageal carcinoma, 8 pts with bronchial/tracheal cancer, 8 pts with other tumours, 9 cases with tracheostomy or tracheal intubation, 8 traumatic cases and 7 consequences with endoscopic therapy (laser, esophageal stent, bronchoscopic apy).

Phistula was covered by tracheal or Y tracheobronchial stent in 19 (38%) pts, esophageal stent in 8 (16%) pts and doublestenting in 4 (8%) pts. Median of overall survival (MOS) was 14.3 m. It was 8.8 m in men and 23.9 m in women (p = 0.044). MOS in malignant diseases was 5.6 m, in benign disease 43.8 m (p = 0.04).

BAE for tracheo-esophageal fistula at one. 17 TS were placed for oeso-bronchial fistula, 5 for bronchial obstruction and 7 consequences with endoscopic therapy (laser, esophageal stent, bronchoscopic apy).

P617 Long-term outcome of bronchial artery embolisation (BAE) for massive haemoptysis
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Objectives: Assess the long-term outcome of bronchial artery embolisation (BAE) for severe haemoptysis.

Methods: We retrospectively identified all patients undergoing BAE from 1994-2007. We collected data from hospital databases and primary care on demographics, respiratory diagnoses and procedure with follow-up of up to 16 years. Outcomes were all-cause mortality and recurrence of haemoptysis requiring repeat BAE.

Results: Of 158 patients who were embolised on 208 occasions. 85 (54%) patients were male and median age was 54 (IQR: 41-67y). The most common underlying diageses were aspergilloma (n=38; 24%) of patients), bronchiectasis (n=24; 15%), unidentifed cause (n=17; 11%) chronic tuberculosis (n=14; 9%), active tuberculosis (n=12; 8%) and cystic fibrosis (n=11; 7%). All-cause mortality at 1 month and 3 years was 5.3% and 29.7%, and need for repeat BAE was 4.7% and 30.7% respectively. Repeat BAE at 3 years was most common with aspergilloma (50%) and least common with active TB (0%). Mean survival was 39.6 months (p = 0.523) and in malignant diseases as well (5.0 m vs 5.6 m, p = 0.484). Endobronchial/endotraheal treatment brings substantial symptomatic relief, but sometimes can be a cause of TEP as well. Other survival determinants could not be analyzed in present study due to small number of patients.

Conclusions: BAE for massive haemoptysis is potentially life-saving with low short-to-medium term failure rates in previous studies. We aimed to characterise patients referred for BAE, to examine long-term treatment success and identify risk factors for requiring repeat BAE. BAE: Bronchial artery embolisation, TS: Total survival.
Introduction: Bronchial artery embolisation (BAE) is the procedure of selective bronchial angiography with embolisation of abnormal vessels.

Aims and objectives: To assess the efficacy and safety of BAE in patients with haemoptysis in pulmonary tuberculosis (PTB).

Methods: This is a retrospective study of all patients of haemoptysis in PTB who underwent BAE between January 2004 and December 2010 in a tertiary care hospital in India. Bronchial arteriography and embolisation was performed using 5 French pigtail catheter and polynyl alcohol (PVA) particles ranging from 150 to 1000 micrometers.

Results: 34 patients (21 males and 13 females) of haemoptysis in PTB, underwent 37 BAE procedures during the period of study. 11 (32.3%) of these patients had multidrug resistant tuberculosis. Mean age of patients was 29.4 years (range: 13-69 years). Indication of BAE was: acute major haemoptysis in 11 (32.3%) and chronic recurrent bleeding in 23 (67.7%) patients. Haemoptysis was successfully controlled after the embolisation procedure in 32 (91.4%) patients. Procedure was repeated in three (8.8%) patients within a period of six months because of recurrent haemoptysis. Following arteries were embolised: right bronchial artery (11), left bronchial artery (7), common bronchial trunk (7), intercostal artery (14), right internal mammary artery (1), thyrocervical trunk (1), right intercostobronchial (2), and left intercostobronchial (1). No abnormal vessel was detected in one patient. The only complication encountered was local haematoma in one (2.94%) patient. Clinical risks were: age (p=0.001), current smoking status (p=0.012), arterial hypertension (p=0.000), chronic arrhythmia (p=0.034), COPD (p=0.000), and stabilized cardiomyopathy (p=0.000). One year survival was 48%, two years survival - 24%.

Conclusion: Repeated BAE with chlorine e6 is a safe and effective for lung cancer patients. Survival depends on degree of endobronchial remission.
84. Rare diffuse lung diseases

P626
Intersitial lung diseases in children: The French national cohort study
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Methods and materials: All patients undergoing LT performed between August 2005 and May 2010 by a single surgeon at our institution were reviewed retrospectively. All airway complications were managed by the Interventional Pulmonary team. Airway stenoses were managed with rigid bronchoscopy, balloon dilation, observation and or stent placement.

Results: A total of 98 patients underwent LT (86 bilateral, 7 left, 5 right). 46 female and 53 male, with a mean age 49.7. 28 patients (28.6%) developed pneumonia within three months of transplantation, 8 of which were identified as a result of pseudomonas (28.6%). 28 (28.6%) patients also reported having evidence of acute cellular rejection within three months after transplantation. The median length of mechanical ventilation after transplant was 3 days (range 1 to 183). Of the 98 patients, 35 (35.7%) developed airway stenosis at a median of 16 weeks (range 1 to 164 weeks following surgery). Of these patients, 23 (>65%) patients received at least one airway intervention.

Conclusions: Airway stenosis after LT can be successfully managed with a variety of airway interventions. Further studies are needed to determine the best modalities.

P625
SHFJV (super imposed high frequency jet ventilation), ETCo2 correlation to PaCO2 in diagnostic and therapeutic rigid bronchoscopy
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Methods and materials: All patients undergoing diagnostic and therapeutic interventional rigid bronchoscopy under SHFJV. Monitoring of the patients included ECG, blood pressure, SaO2, EtCO2, arterial blood gas analysis, FIO2 jet, FiO2 aw.

Results: 23 Pediatric Department, Centre Hospitalier Universitaire de Tours, Tours, France; 2Pediatric Department, Centre Hospitalier Universitaire de Reims, Reims, France; 2UMR S-707, INSERM, Paris, France

Introduction: In France rare orphan diseases as pediatric interstitial lung diseases (ILDs) have been identified as a public health priority. A national pediatric reference center for rare lung diseases, Respilare, was created several years ago.

Objective: To investigate the prevalence and the expression of pediatric ILDs within a national cohort in France.

Methods: Children presenting with ILD from 1995 to 2010 were identified through the Respilare network. Clinical, radiological, functional, pathological, biological and genetical longitudinal data were collected by the physicians in charge of ILDs patients using a unique national biomedical database.

Results: Data were available for 197 children presenting with ILD. The mean incidence was 26/year. Median age at diagnosis was 20 months [0-16 years], and the sex ratio was 0.87 male/female. Investigations including thoracic high resolution computed tomography scan (n=197), broncho-aveolar lavages (n=97), lung biopsies (n=30) and analysis of surfactant genes (n=67) led to a diagnosis for 142 out of the 197 children (63.4%): surfactant mutation associated disorders (n=29), 14.7%, haemosiderosis (n=24, 12.2%), sarcoidosis (n=20, 10.2%) and alveolar proteinosis (n=17, 8.6%) were the most common diagnoses. Pulmonary hypertension was observed in 16% of cases.

Conclusion: A national database is now used in France for pediatric ILDs and facilitates clinical studies. Based on this experience, recommendations for diagnosis and therapeutic strategies are being established. As a European ILDs consortium is emerging, a European ILDs registry would be the next step to improve the knowledge of pediatric ILDs pathophysiology and their management.

P627
Diagnostic value of serum VEGF-D in consecutive patients with lymphangioleiomyomatosis
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Methods: Serum levels of VEGF-D were measured prospectively in 45 patients the diagnosis of LAM.

Results: Serum VEGF-D levels were significantly higher in patients with LAM compared to healthy controls (p<0.0001). VEGF-D was elevated (860 pg/mL) in only one patient with Birt-Hogg Dubé disease with the mutation PQ385X in the FLCN gene, with LAM ruled out by lung biopsy. Using 800 pg/mL as a threshold, the specificity of VEGF-D was 98% but sensitivity was only 76%. VEGF-D in LAM was >800 pg/mL in 57 patients, contributing to the diagnosis of LAM with false positive only rarely encountered (as in Birt Hogg Dubé disease). Serum VEGF-D level may remain elevated in transplanted patients and those receiving medical therapy.

Conclusion: Serum VEGF-D levels greater than 800 pg/mL contribute to the diagnosis of LAM with false positive only rarely encountered (as in Birt Hogg Dubé disease). Serum VEGF-D level may remain elevated in transplanted patients and those receiving medical therapy.

Financial support: CNMR and FP7 of the European Commission.
P628
Extracellular concentration and enzyme activity of proteasome in BAL of patients with alveolar proteinosis

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Introduction: Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by alveolar accumulation of surfactant lipoproteins. Proteasomes are responsible for nonsyndromal protein degradation. They are involved in apoptosis, stress response and inflammation. ARDS and sarcoidosis show elevated levels of extracellular protease. The aim of this study was to detect proteasome concentration and enzyme activity in BALF in PAP.

Patients and methods: 22 PAP patients (20 with primary, 2 with secondary form) and 18 healthy controls were studied. 205 proteasome subunit (murine monoclonal antibody by Biomol Int. L.P., Exeter, UK) was measured by ELISA in BALF. The cleavage of 3 fluorogenic substrates (Suc-LVY-AMC, BZ-VGR-AMC and Suc-LLE-AMC) was used to describe the specific enzyme activity (cymotryptsin-, trypsin- and caspase-like) of extracellular proteasome.

Results: Proteasome concentration in BALF of PAP patients was 10-fold higher than in healthy subjects (659±422 vs 60±36 ng/mL, p<0.0001). Trypsin- and caspase-like activity of proteasome was significantly increased in PAP compared to healthy subjects (BZ-VGR-AMC 1.5±0.9 vs 0.2±0.15, 27 Suc-LLE-AMC 0.62±0.1 vs 0.07±0.06 pkat/mL; p<0.01). Enzyme activity for all 3 substrates correlated directly with the total protein concentration in BALF (r=0.7, p=0.002; r=0.56, p=0.03), inversely with TLCO (r=0.72, p=0.008; r=0.7, p=0.014; r=0.73, p=0.006).

Conclusions: Proteasome alveolar concentration is higher in PAP than in healthy controls. This is associated with increased trypsin- and caspase-like enzyme activity. Proteasome seems to be significantly involved in the alveolar protein degradation in PAP.

P629
Chronic eosinophilic pneumonia after radiation therapy for breast cancer

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Background: Several reports have documented the possible appearance of organising pneumonia (OP) as complication of radiation therapy (RT) for breast cancer, but only one has described the occurrence of chronic eosinophilic pneumonia (CEP) in this setting (Cottin V. et al. Eur Respir J 2004, 23:9-13).

Methods and results: We describe 3 new cases of CEP developed after RT for breast cancer. The median time interval between the end of RT and onset of CEP was 4.3 months. All patients were symptomatic for fever or dry cough. None had history of allergy, one was an active smoker. Chest CT showed multiple areas of alveolar consolidation in regions not limited to the irradiated lung. None of the patients had blood eosinophilia >1 G/L. In all cases, the bronchoalveolar lavage (BAL) differed only of a modest eosinophilia (25%, 25, 45 and 90% respectively). The respiratory function tests showed normal lung volumes and reduced carbon monoxide transfer factor to 60% predicted in 2 patients. All patients had rapid resolution of symptoms with corticosteroid therapy. 2 patients experienced 2 relapses each after treatment withdrawal. In all patients, therapy could be stopped after a median time of 16 months. All are disease-free after a median time of 85 months.

Conclusions: We confirm the possible onset of CEP as expression of lung injury induced by RT for breast cancer. In contrast to previous observations, CEP after RT may occur in the absence of blood eosinophilia and history of asthma. Since CEP and OP after RT have similar clinical pictures, CEP may be misdiagnosed as OP if BAL is not performed.

Results: We enrolled 76 PAP patients from 1989 to 2011, divided as follows: Idiopathic PAP (n=70) of which the autoimmune nature was confirmed in 76%, Secondary PAP (n=3, 4%), Congenital PAP (n=11, 1.3%) and PAP-like disorders (n=2, 2.7%). The idiopathic PAP was mainly observed in males (72.8%) over females, with a mean age at diagnosis of 40.7±13. A smoking history (current or former smokers) occurred in 68.5%, with a mean of 27packyears/years. The most common presenting symptom was dyspnea, alone (27 patients) or in combination with cough (16 patients). 4 patients were completely asymptomatic. Intercurrent infections were present in 14 cases. Mean GMAs level was 261±240 μg/mL (< 3 μg/mL). From our whole series, 43 patients were submitted to WLL: 30 (43%) received 1 WLL, whereas 13 (30%) received 2 or more WLLs. Comparison of pulmonary function testing data between not lavaged and lavaged PAP patients showed a significant difference for the TLC%O2 (r= -0.76 ± 18.84 vs vs 46±1.37, p=0.01) and for the A-AO2 gradient (r= 17.8±17.9 vs 45±15.8 mmHg, p=0.043). Conclusion: The establishment of a reference center for PAP in Italy has allowed to gather and well characterize one of the largest series of PAP patients worldwide. Funding: AIF (FAR7M3C19K), eRARE (EaPAPNet).

P631
Lymphocytes populations in bloods and lungs in patients with auto-immune pulmonary alveolar proteinosis

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Background and aim: Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by accumulation of lipoproteinaceous material within alveolar spaces. The clinical course of PAP ranges from spontaneous resolution of symptoms with corticosteroid therapy. 2 patients experienced 2 relapses each after treatment withdrawal. In all patients, therapy could be stopped after a median time of 16 months. All patients were symptomatic for fever or dry cough. None had history of allergy, one was an active smoker. Chest CT showed multiple areas of alveolar consolidation in regions not limited to the irradiated lung. None of the patients had blood eosinophilia >1 G/L. In all cases, the bronchoalveolar lavage (BAL) differed only of a modest eosinophilia (25%, 25, 45 and 90% respectively). The respiratory function tests showed normal lung volumes and reduced carbon monoxide transfer factor to 60% predicted in 2 patients. All patients had rapid resolution of symptoms with corticosteroid therapy. 2 patients experienced 2 relapses each after treatment withdrawal. In all patients, therapy could be stopped after a median time of 16 months. All are disease-free after a median time of 85 months.

Conclusions: We confirm the possible onset of CEP as expression of lung injury induced by RT for breast cancer. In contrast to previous observations, CEP after RT may occur in the absence of blood eosinophilia and history of asthma. Since CEP and OP after RT have similar clinical pictures, CEP may be misdiagnosed as OP if BAL is not performed.

P632
Old and novel surfactant protein (SP-C) mutations in children

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Genetic variations of SP-C gene are known to cause interstitial lung disease. In previous studies 55 patients have been described focusing on the genetic abnormalities and clinical course. Here we report the data of children with SP-C mutations collected between 1998 and 2010. Lung biopsy findings and previous radiological imaging studies were re-examined using up to date classifications. All 11 children identified had heterozygous mutations in the SP-C gene, six of which carriedT37 and five other mutations (H59R, G47D, C121F, E191X, A112T). Age at onset of symptoms varied from birth to 11 years; however most presented with postnatal respiratory distress syndrome or later with tachypnea, cough and failure to thrive. Chest computer tomography showed a variety of different patterns including ground glass attenuation, mosaic pattern, lung fibrosis and cysts. Initial diagnosis was made by genetic testing alone in 6 of 11 cases and by lung biopsy in 5 patients. Histology pattern included non specific interstitial pneumonia and desquamative interstitial pneumonia, chronic pneumonia of infancy, pulmonary alveolar proteinosis and end stage fibrosis. Average follow-up was 7 years (0.8-
P633
Serum VEGF-D and VEGFR-3 are biomarkers in lymphangioleiomyomatosis for its diagnosis and impaired pulmonary function

Methods: We measured VEGF-C, VEGF-D and VEGFR-3 in serum of patients with LAM. In patients with LAM, 4 patients with chronic obstructive pulmonary disease (COPD), and 6 normal subjects by enzyme-linked immunosorbent assays, and compared them with pulmonary function tests.

Results: In patients with LAM, serum VEGF-D levels were significantly increased (2995.1±992.2 pg/ml) compared with patients with COPD and normal subjects (264.7±157.7 pg/ml, respectively). Serum VEGF-C and VEGFR-3 levels were also significantly increased in LAM (4511.3±746.7 pg/ml) compared with normal subjects (2633.8±304.1 pg/ml). In patients with LAM, serum VEGF-D levels were negatively correlated with FEV1/FVC (rs=-0.8360; p=0.0269) andDLCO/VFVC (rs=-0.04976; p=0.0035), and serum VEGFR-3 levels were negatively correlated with FEV1/FVC (rs=-0.8119; p=0.0498).

Conclusions: This result indicates that, in LAM, serum VEGF-D and VEGFR-3 are candidate for biomarkers for the diagnosis and impaired pulmonary function.

P634
Lymphangioleiomyomatosis – Clinical characteristics and longitudinal follow-up of 36 cases
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Patients with lymphangioleiomyomatosis (LAM) are evaluated with multi-directional assessments in the same manner as those with COPD, but the pulmonary physiological features in patients with end-stage pulmonary LAM are complicated because the severe condition of patients caused by disease progression prohibits extensive testing. To complement this, we applied a forced oscillation technique (FOT) for the assessment of patients with LAM, and evaluated the relationship between respiratory impedance and disease severity.

Methods: 9 subjects with LAM were studied cross-sectionally. Lung function tests and respiratory impedance were measured. A concept based on the Helmholtz Resonator was used to interpret those respiratory mechanics. A simple 3-element series (RIC) model was used to estimate airway resistance (Raw), airway iner-
tance (Jaw), and respiratory compliance (Crs) and resonant frequency (fres). For the estimation of disease severity, a multifunctional index (BODE index) was used.

Results: The respiratory impedance spectra were fitted to the RIC model, and each value of goodness of fit from the 9 subjects was over 0.9. Raw, Jaw and fres correlated with 0.66, 0.7 and 0.7 respectively. For the BODE index, Crs correlated with Jaw.

Conclusions: The RIC model corresponding with the Helmholtz Resonator provides a reasonable physiological interpretation in which all mechanical param-
ters reflected airway obstruction and a decrease in capacitative behavior. Thus, non-invasive FOT are useful and represent a potential monitoring tool to evaluate disease severity and prognosis in a cohort of patients with LAM.

P635
Relationships between respiratory impedance and prognosis in patients with end-stage pulmonary lymphangioleiomyomatosis: A concept based on the Helmholtz resonator

Methods: We measured VEGF-C, VEGF-D and VEGFR-3 in serum of 7 patients with LAM, 4 patients with chronic obstructive pulmonary disease (COPD), and 6 normal subjects by enzyme-linked immunosorbent assays, and compared them with pulmonary function.

Results: In patients with LAM, serum VEGF-D levels were significantly increased (2995.1±992.2 pg/ml) compared with patients with COPD and normal subjects (264.7±157.7 pg/ml, respectively). Serum VEGF-C and VEGFR-3 levels were also significantly increased in LAM (4511.3±746.7 pg/ml) compared with normal subjects (2633.8±304.1 pg/ml).

Conclusions: This result indicates that, in LAM, serum VEGF-D and VEGFR-3 are candidate for biomarkers for the diagnosis and impaired pulmonary function.
P638
Long term follow-up in patients with pulmonary alveolar proteinosis
Yuliia Ilkovich, Lubov Novkova, Olga Baranova, Ivetta Dvortakovskaya, Andrey Bazhanov, Research Institute of Pulmonology, Pavlov State Medical University, St. Petersburg, Russian Federation

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by respiratory failure due to surfactant accumulation within the lung. PAP is currently treated by whole lung lavage (WLL).

Since 1977, our cohort is 52 (35 male, 17 female) idiopathic PAP patients. Median age - 37±6 y.o. Most patients are current or former smokers (64%) and have occupational history (55%). Most patients have moderate impairments in functional parameters (mean DLco - 65±15% pred., mean pulmonary artery systolic pressure - 30±6 mm Hg).

The majority of patients (88.4%) received WLL therapy. 3 patients (5.8%) had segmental lavage. 3 patients (5.8%) - N-acetylcysteine (NAC) as monotherapy. The average number of WLL procedures was 2 (1-7). 34.6% received only one WLL and demonstrated long-term improvement after the procedure.

5-years survival rate is 100%. Spontaneous resolution was observed in 2 patients (3.8%) on NAC treatment. In most cases the course of PAP was slowly progressive. 8 patients (15.4%) had rapid progressive deterioration with respiratory failure despite repeated WLL. Predictors of fast progression were estimated. No associations with gender, age, smoking status were found. Long antibiotics and corticosteroids (CS) intake due to incorrect diagnoses before PAP diagnostic (< 0.05) and more than 3 years since first symptoms occurred till PAP diagnostic (< 0.05) correlated with progressive deterioration despite repeated WLL treatments. Besides, long CS intake increased the risk of secondary infections: pneumonia in 3 patients (5.8%), tuberculosis in 3 patients (5.8%), aspergillosis – 1 patient (1.9%).

Avoiding of delayed diagnosis/incorrect treatment increases the probability of long symptom-free period after WLL.

P639
Lymphocytic interstitial pneumonia – Two cases of unusual presentation
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Background: The diagnosis of Lymphocytic Interstitial Pneumonia (LIP) is established by the demonstration of an exuberant lymphoid infiltrate. The ATS/ERS statement includes it in the group of idiopathic interstitial pneumonias on the basis that rare cases of histopathological LIP pattern are truly idiopathic.

Case 1: 56-year old male admitted with hemoptysis. Thoracic imaging showed a 1.8 cm solitary nodule in the right upper lobe. Bronchoscopy was negative for malignancy. PET-CT Scan revealed increased uptake. Thoracic surgery and histology revealed dense lymphocytic infiltrate in alveolar septa. Further testing ruled out subjacent causes of LIP.

Case 2: 57 year old female admitted for progressive dyspnea. Chest CT revealed lung fibrosis and honeycombing mainly in the upper lobes. There was no evidence of malignancy. PET-CT Scan revealed increased uptake. Thoracic surgery and histology revealed dense lymphocytic infiltrate in alveolar septa. Further testing ruled out subjacent causes of LIP.

Comment: LIP represents a benign polyclonal proliferation that can diffusely involve the lung or be a focal process. The combined presence of nodules, cysts and ground glass are suggestive of LIP. Presentation as a solitary pulmonary nodule is rare; it may represent focal involvement of the lymph proliferative disorder. The histological pattern obtained by surgical biopsy was consistent with LIP with areas of interstitial fibrosis. Secondary causes of LIP were excluded. Treatment with prednisolone was started with clinical and functional improvement.

P640
Abnormalities between down regulation of cyclooxygenase-2 and up-regulation of grow factors in patients with systemic sclerosis
Edwin Roger Parra, Flavia Lin, Vera Capelozzi. Pathology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

The main of this study was observed the relationship between COX1, COX2, bFGF, TGFb and apoptosis and TUNEL expression. The expression of these markers was started with their pulmonary function tests.

The objective is to study features of pulmonary involvement in patients with diffuse connective tissue diseases.

Materials and methods: Retrospective cohort study of 1363 patients. Inclusion criteria: patients at the age of 17-70 with diffuse connective tissue diseases. Exclusion criteria: maligna neoplasms of any location, concomitant bronchopulmonary pathology. Standard clinical examination, electrocardiography, echocardiogram, spirometry, X-ray study, high resolution computed tomography, ultrasonic scanning of pleural effusion.

Results: The involvement of respiratory system was found in 56 (4,11%) of 1363 examined patients. The patients with systemic lupus erythematosus - 25 (44.6%) and rheumatoid arthritis - 19 (33,9%) prevailed. Fewer cases of pulmonary involvement were met in patients with systemic sclerosis - 9 (16,1%), overlap-syndromes - 2 (3,6%) and idiopathic dermatomyositis- 1 (1,8%). The most common manifestations of pulmonary involvement are bronchocclusive syndrome - 39,5%, pulmonary fibrosis – 23,2%, pleuritis – 16,1% and pneumonitis - 12,5%. In 3,6% cases vasculitis and in 1,8% - combinations of pleuritis-pneumonitis, pleuritis- bronchocclusive syndrome and pneumonitis- pleuritis- pulmonary fibrosis were diagnosed.

Conclusion: In 4,11% cases, diffuse connective tissue disorders are accompanied with the involvement of respiratory system that is commonly manifested by bronchocclusive syndrome, pulmonary fibrosis and pleuritis.

P642
Arterial stiffness in systemic scleroderma patients with restrictive lung disease
Nina Karoli, Andrey Rebrev, Hospital Therapy Department, Saratov State Medical University, Saratov, Russian Federation

Systemic sclerosis (SSc) is a chronic disease of unknown etiology, characterized by enhanced fibrosis, and microvascular abnormalities.

To study the stiffness of large arteries in relation to the restrictive lung disease (RDL) aortic stiffness was examined in patients with systemic sclerosis (SSc). 27 non-smoking patients (52,48±7,18 yrs) with diagnosis of SS were included. 17 patient was with RLD (FVC<70%) and 10 patient with normal lung function. Control group consisted of 28 healthy persons, aged 49,82±8,33 years. Arterial stiffness parameters were measured by means of pulse wave analysis using Ten-sioMed Arteriograph (TensioMed, Hungary). Following parameters were factored: aortic augmentation index (AlxAo), aortic pulse wave velocity (PWV), brachial artery augmentation index (AlxB), central blood pressure (SBPao).

Arterial stiffness in patients with sclerosis

<table>
<thead>
<tr>
<th></th>
<th>SS with RLD (n=17)</th>
<th>SS without RLD (n=10)</th>
<th>Controls (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlxAo%</td>
<td>-3.4±3.32*</td>
<td>-10.1±14.09*</td>
<td>-24.7±8.0±15</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>10.0±9.2*</td>
<td>9.25±2.05</td>
<td>8.44±2.44</td>
</tr>
<tr>
<td>Index AlxAo/AlxB</td>
<td>1.97±3.14***</td>
<td>1.46±2.56**</td>
<td>-1.5±2.47</td>
</tr>
<tr>
<td>Index PWV/AlxB</td>
<td>0.4±0.83***</td>
<td>0.5±0.77***</td>
<td>-0.5±0.64</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-20.4±9.26*</td>
<td>-2.5±7.98</td>
<td>-7.5±7.25</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>99.3±6.46</td>
<td>97.9±5.46</td>
<td>95.9±6.33</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 with controls. Index CP = (SBPao) / (brachial systolic BP) × 100.
85. What is new in the approach to pulmonary fibrosis?

**Intravascular Lung Pres.:** Chronic conditions such as pulm. fibrosis lead to pulmonary arterial hypertension (PAH) and worsen with only a 3-year survival. The increase in mortality is due to progression of disease, worsening of functional capacity, and to treatments that improve symptoms but worsen pulmonary function. This intravascular lung pres. is due to an increase in pulmonary vascular resistance. The main objective is to improve pulmonary function with a combination of PAH and pulmonary function.

**Conclusion:** We have found a significant improvement in pulmonary function with a combination of PAH and pulmonary function.
Arterial stiffness and endothelial dysfunction in idiopathic pulmonary fibrosis (IPF)

Sergey Andreev, Makara Makarova, Alexander Chuchalin. Clinical Department, Pulmonary Research Institute, Moscow; Russian Federation

Background: Fibrotic lung diseases are associated with an increased prevalence of coronary artery disease and cardiovascular complications [Kizer et al., 2004]. Arterial stiffness and endothelial dysfunction are widely accepted as markers of cardiovascular risk.

Objectives: The aim of the present study was to assess aortic stiffness and endothelial dysfunction in patients with IPF and to determine the association of these markers with other clinical and functional parameters.

Methods: We enrolled 25 IPF patients (age 57±8 yrs, FVC 80±18%; DLco 38±15%) and 30 normal control subjects (age 52±5 yrs). Assessment of arterial stiffness was performed by use of digital photoplethysmography (Pulse Trace PCA 2, Micro Medical). Change in reflection index of the digital volume pulse in response to salbutamol (ΔRI alignSelf) was used to assess endothelial function.

Results: In IPF patients stiffness index (SI) was significantly higher than in normal control subjects: 9.8±3.1 vs 6.0±1.0 m/s (p<0.001). The correlations between SI and sleep time spent with SpO2 <88% (r=0.67, p<0.05) and total serum cholesterol level (r=0.77, p<0.05) were highly significant in IPF patients. ΔRI alignSelf was significantly lower in IPF patients than in control subjects: 2.2±1.2% vs 15.8±9.3% (p<0.01). ΔRI alignSelf was significantly associated with FEV1 (r=-0.57, p<0.05), mean nocturnal SpO2 (r=0.83, p<0.05) and total cholesterol level (r=0.71, p<0.05).

Conclusions: Arterial stiffness and endothelial dysfunction are significantly impaired in IPF patients. Decreased FEV1 was associated with endothelial dysfunction. Nocturnal hypoxemia and total cholesterol level have an association with both arterial stiffness and endothelial function.

Clinical course of idiopathic pulmonary fibrosis (IPF): Prediction and outcome

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Background: IPF is a progressive disease for which a median survival time of 2.8 years was reported. However the clinical course of IPF is variable. Acute exacerbation (AE) is a major cause of death in IPF, but only a minority of patients develop AE.

Objectives: The aim of this study was to examine different clinical courses of IPF and to evaluate associated risk factors and predictors.

Methods: We retrospectively studied 85 consecutive patients diagnosed with IPF based on the criteria of the ATS/ERS consensus statement. Clinical data and serial pulmonary function tests were obtained. In accordance to King et al. (King, TE et al. AJRCCM 2011; 183:431-40) patients were grouped to four clinical phenotypes: stable disease, slowly progressive, rapid progressive to death or mixed course. Furthermore, AEs as defined by the criteria of Collard et al. (Collard, HD et al. AJRCCM 2011; 183:431-40) patients were grouped to four clinical phenotypes: AaDO2 ≥ 30, 8% within 6 months; AaDO2 ≥ 10% within 6 months; initial AaDO2 (ΔAaDO2) ≥ 10% within 6 months; initial AaDO2 (ΔAaDO2) ≥ 10% within 6 months.

Results: Of 85 IPF patients 34 (40%) patients, with multiple episodes in 6 (7%) patients. The 5-y survival rate of IPF patients with and without AE was 15% and 41%. Baseline CCL18 serum concentrations differed significantly between the four clinical phenotypes (p<0.0001). IPF patients with a progressive or mixed course showed higher CCL18 serum concentrations (p<0.0001), lower FVC predicted (FVC<60%; p<0.0156) and lower TLC predicted (p=0.002). Stepwise multivariate regression analysis of all patients revealed that CCL18 serum concentration (p=0.016) was independently associated with AE.

Conclusions: We demonstrate that baseline serum CCL18 levels are elevated in IPF patients prone to AE and predict a rapid progressive or mixed course of IPF.

Risk factors of acute exacerbation of idiopathic pulmonary fibrosis-extended analysis of the pirfenidone trial in Japan

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Background: Although acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is a well known clinical condition, predicting risk factors remain unknown. Recent studies reported that various baseline factors, and at least 10% decline in FVC at six months were reported as risk factors for AE (Sarcoidosis Vasc Diffuse Lung Dis 2010;27:103-110). We sought to evaluate the risk factors of AE by analyzing our phase III clinical trial of pirfenidone for patients with IPF (n=275; Eur Respir J 2010; 35: S21-9).

Methods: Baseline characteristics including age, sex, smoking, BMI, dyspnoea grade (HUGH-JONES classification), AaDO2, PaO2/Δc, DLco, KL, SP-A, SP-D were evaluated as possible risk factors for AE. Decline of VC≥10% within 6 months was also evaluated. In addition, effect of pirfenidone therapy was also evaluated.

Results: During 52 weeks, 14 patients experienced AE-IPF. Univariate analysis by Cox proportion hazards model were as follows: age (HR, 0.982, p=0.642), sex (HR, 1.505, p=0.489) smoking (HR, 1.046, p=0.168), BMI (HR, 0.935, p=0.460), dyspnoea grade (HR, 1.763, p=0.168), AaDO2 (HR, 1.047, p=0.069), PaO2 (HR, 0.955, p=0.110), Δc/Vc (HR, 0.971, p=0.078), DLco (HR, 0.994, p=0.714), KL-6 (HR, 1.000, p=0.698), SP-A (HR, 0.989, p=0.776), SP-D (HR, 1.000, p=0.875), pirenidone treatment (HR, 0.611, p=0.722). Decline of VC was a significant risk factor for AE-IPF (HR, 3.780, p=0.014). Stepwise multivariate analysis revealed that initial AaDO2 (HR, 1.055, p=0.045) and decline in VC in 6 months (HR, 3.951, p=0.012) were significant risk factors for AE-IPF.

Conclusions: Baseline higher AaDO2 and decline of VC≥10% within 6 months are significant risk factors of AE-IPF.
P651 Effects of nitric oxide synthase up-regulation in early remodeling of usual interstitial pneumonia has impact on long term outcome of patients

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Recently, impaired endothelial-dependent vascular tone suggest that NOS enzymatic activity, as well as vascular NO synthesis and release, may decrease or increase depending on early or late pulmonary remodeling process. In this study, we validated the importance of the expression of NOS isoforms (neuronal [nNOS], inducible [iNOS], and endothelial [eNOS]) protein and studied the relationships between NOS isoforms in early and late remodeling of usual interstitial pneumonia (UIP).

Material and methods: We determined density of endothelial, muscular, myofibroblasts and alveolar cells expressing NOS in surgical lung biopsies from 25 patients with UIP. We used immunohistochemistry and histomorphometry to evaluate the amount of endothelial, muscular, myofibroblasts and alveolar cell staining for NOS.

Results: Unaffected areas of UIP had increased eNOS and iNOS expression, whereas a significant increase of NOS expression was found in unaffected and vascular areas. Kaplan–Meier analysis for NOS and eNOS dichotomized percentiles revealed respectively a statistically significant prolonged disease specific survival for patients in the low risk group (estimated median survival 51.7 vs 33.36 and 55.56 vs. 9.87 months for the high risk group, log rank p<0.01).

Conclusions: We conclude that the presence of a vascular remodeling is associated with vascular injury and with a global correlation test, p=0.04). We postulated that CEC and all EPC subtypes might be differently modulated in IPF. We aimed at 1) assessing them in early stages of IPF and 2) searching for correlations with disease severity.

Methods: 64 consecutive patients with newly diagnosed IPF and 10 healthy age-matched volunteers were studied. CEC were isolated with CD146-coated beads. CD34, CD133 and KDR antigens, characterizing EPC, were assessed through flow cytometry. EPC (early CFU-Hill and late endothelial cells forming colonies (ECFC) were also counted using cell culture. Results: CEC numbers were significantly increased in IPF (p=0.004) whereas EPC assessed using both flow cytometry (CD34+CD133+) and cell culture were decreased vs controls (p<0.05). CEC did not differ according to disease severity (DLCO > 85% or < 85%) nor did CD34+KDR+ cells. In contrast, progenitors obtained in culture were markedly increased in the most severe vs the least severe IPF subgroup (p=0.04 and p<0.01 for CFU-Hill and ECFC, respectively, for DLCO<85% vs >85%). ECFC was the only cell type found to be correlated to DLCO (Spearman correlation test, p=0.04).

Conclusion: IPF is associated with markers of vascular injury and with a global decrease in EPC. Disease severity is associated with an EPC mobilization whose mechanisms and clinical impact need to be explored.

P652 Imbalance between circulating endothelial cells and endothelial progenitors in idiopathic pulmonary fibrosis

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Background: Fibrogenesis during idiopathic pulmonary fibrosis (IPF) is associated with abnormal vascular remodeling. Respective abundance of circulating endothelial cells (CEC) and endothelial progenitor cells (EPC) might reflect the balance between vascular injury and repair and potentially serve as a biomarker of the disease.

Objectives: We postulated that CEC and all EPC subtypes might be differently modulated in IPF. We aimed at 1) assessing them in early stages of IPF and 2) searching for correlations with disease severity.

Methods: 40% of CD34+CD133+ cells were significantly increased in IPF (p=0.004) whereas EPC assessed using both flow cytometry (CD34+CD133+) and cell culture were decreased vs controls (p<0.05). CEC did not differ according to disease severity (DLCO > 85% or < 85%) nor did CD34+KDR+ cells. In contrast, progenitors obtained in culture were markedly increased in the most severe vs the least severe IPF subgroup (p=0.04 and p<0.01 for CFU-Hill and ECFC, respectively, for DLCO<85% vs >85%). ECFC was the only cell type found to be correlated to DLCO (Spearman correlation test, p=0.04).

Conclusion: IPF is associated with markers of vascular injury and with a global decrease in EPC. Disease severity is associated with an EPC mobilization whose mechanisms and clinical impact need to be explored.

P653 Leptin and adiponectin levels in idiopathic pulmonary fibrosis

Foteini Malli1, Panagiotis Georgoulis1, Vasilassou Varvara2, Irene Tsiliomi1, Konstantinos Georgoulis1, Zoe Daniil1, 1Hematology Department, University of Thessaly School of Medicine, Larissa, Greece; 2Nuclear Medicine Department, University of Thessaly, Larissa, Greece

Background: Studies in the literature suggest a regulatory role of adipokines in the development of fibrosis in various organs. Leptin is a critical factor for the development of fibrosis in the liver. In contrast, adiponectin inhibits liver fibrogenesis both in vivo and in vitro. However, their role in pulmonary fibrosis has not been examined in the past.

Objectives: We hypothesized that leptin and adiponectin may be involved in the development of pulmonary fibrosis and therefore we measured levels of leptin and adiponectin (RIA) in the serum of 37 Idiopathic Pulmonary Fibrosis (IPF) patients (mean±SD: 68.8±8.8 years) and 22 controls (65±7.5 years). Clinical and radiological data were collected from all subjects. Pulmonary function tests, arterial blood gas analysis and thoracostrophic echocardiography were performed.

Results: The levels of leptin and adiponectin did not differ between patients and controls. However, leptin levels when divided by BMI in male patients with PaO2 <65 were significantly reduced as compared to male patients with PaO2 >65 mmHg (0.21 vs 0.38, p=0.031, respectively). Additionally, leptin to adiponectin ratio in male IPF patients with <65 mmHg was significantly reduced versus male patients with PaO2 >65 mmHg (1.07 vs 1.45, p=0.045, respectively).

Conclusions: Leptin levels when adjusted for BMI and leptin to adiponectin ratio are reduced in male IPF patients with hypoxia. Our findings suggest a possible role of leptin in the severity and/or pathogenesis of IPF. Further studies are required in order to clarify the association of leptin and adiponectin with the disease.

P654 HCRT score to control and evaluate the prognosis in idiopathic pulmonary fibrosis

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Introduction: HCRT is not commonly used to assess the severity of idiopathic pulmonary fibrosis (IPF).

To assess: We sought to evaluate the usefulness of a semiquantitative HCRT score and its relation with respiratory function tests normally used to ascertain IPF severity and to monitor the evolution and progression of the fibrotic process.

Patients and methods: A prospective 4 years study including 36 consecutive IPF patients. A semiquantitative score was used to score every predefined IPF 4 parameters on HCRT. As a result of summing up all of them we had the Total Score of Fibrosis for each patient.

Results: We studied its relation with functional respiratory tests, bronchoalveolar lavage (BAL) cellularity and analytically the differences found among the death patients.

Methods: We found a significant correlation between the honeycomb score and% DLCO (r= -0.48, p=0.004), total score of fibrosis with% FEV1 (r= -0.41, p=0.01),% TLC (r= -0.41, p=0.01) and% DLCO (r= -0.41, p=0.01) and% TLC (r= -0.36, p=0.03). The 6-minutes walking test (6MWT): the final SaO2 correlated with the total score (r= -0.48, p=0.04). A+2grad also correlated with the honeycomb score (r=0.43, p=0.01) and the total score (r=0.48, p=0.005). Dead patients had a higher total score and a tendency of higher neutrophilia in BAL (p=0.059).

Conclusions: A semiquantitative score of HCRT is useful in assessing the initial severity of IPF and should be able to predict its development.

P655 Daily hand-held spirometry for the monitoring of patients with idiopathic pulmonary fibrosis

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Introduction: Idiopathic pulmonary fibrosis (IPF) is an invariably fatal condition characterised by a variable course; prolonged periods of apparent disease stability are often interspersed by dramatic and often cryptogenic acute deteriorations. These acute exacerbation are a significant cause of morbidity and mortality in IPF. For lung transplant recipients, daily hand held spirometry has been shown to be an effective means of detecting acute rejection episodes. This exploratory study aims to determine the utility of daily hand held spirometry in IPF.

Methods: Patients with IPF were recruited from amongst new referrals to our unit. Baseline severity was assessed by FVC, DLco and 6 minute walk. Patients were given a hand held spirometer (Carefusion, UK) and provided with instruction on how to self-administer spirometry. Patients were asked to record daily FEV1 and FVC values.

Results: To date, 19 subjects have been recruited; 17 male, age 66.5±7.6 years (mean± SD). Overall the subjects have moderate to severe disease with FVC 74.2±21.8% predicted, DLco 40.6±13.5% predicted and 6 minute walk distance 526±120m. For subjects thus far completing over 4 weeks of diary monitoring (n=49), mean hand held FVC correlates well with formal clinic spirometry (r=0.57).
**P656**

**Slow versus rapid progressors in idiopathic pulmonary fibrosis**

Filipca Soares Pires, Carla Damas, Patricia Motã, Natãlia Melo, Diego Costa

**Background:** Idiopathic pulmonary fibrosis (IPF) is usually characterized by the insidious onset of dyspnea or cough, but there is a subgroup of patients who display a rapid progression to an end-stage disease. These two phenotypes, slow progressors (SP) and rapid progressors (RP), have not yet been fully characterized.

**Aims:** To characterize SP and RP and identify baseline factors predicting each progression.

**Methods:** A retrospective study with 81 IPF patients was performed. They were classified into SP and RP according to the rate of decline of FVC over 12 months (6% or ≤ 12% per year) and the rate of decline of 6 minute walk distance (≤ 50%, ≤ 350 m). The Kaplan-Meier survival curve was used to evaluate survival differences between SP and RP.

**Results:** The group was divided into SP and RP. The comparison between the two groups showed lower median values of FVC (60 versus 73) and TLC (57.8 versus 72) and a higher percentage of non-smokers in RP group at time of diagnosis.

**Conclusion:** The analysis of this group of IPF patients confirms two clearly separated phenotypes, SP and RP, that must be discriminated, since they seem to have different presentations and a remarkably different evolution. These results could mean distinct physiopathological pathways, which could implicate different therapeutic approaches.

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**P657**

**Clinical picture analysis of idiopathic pulmonary fibrosis (IPF) and lung cancer (LC) concomitantly in the population of patients hospitalized in 1st Clinic of Lung Diseases Institute for Tuberculosis and Lung Diseases in Warsaw, Poland in the years 1994-2009**

Agnieszka Buraczewska, Wojciech Skorupa, Jan Kus, Anna Kempisty, Iwona Bartoszuk

**Background:** In idiopathic Pulmonary Fibrosis parenchymal lung damage leads to defects in mechanics and gas exchange, manifesting with progressive dyspnea and exercise limitation. Since IPF carries a poor prognosis, early and reliable prediction of survival is of significant value to the clinician. The role of maximal exercise data in prognostic evaluation of IPF patients is uncertain.

**Aims and objectives:** The aim of the present study was to evaluate the prognostic significance of cardiopulmonary exercise test (CPET) in this group of patients.

**Methods:** Twenty five IPF patients were prospectively recruited and underwent functional evaluation through maximal (CPET) and submaximal exercise testing. Six minute walk test (6MWT) at diagnosis. Patients were followed up regularly; epidemiologic and survival data were gathered. Correlations between survival and parameters of maximal and submaximal exercise were calculated.

**Results:** Mean survival was 44.4 months.

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**P659**

**The prognostic significance of cardiopulmonary exercise in IPF**

Christina Triantafillidou, Panagiotis Lyberopoulos, Liokourgos Kolilekas, Konstantinos Kagouridis, Sotirios Gytopoulos, Christina Sotiriopoulou, Anastasia Kotanidou, Anna Karakatsani, Spyros Papiris.

**Background:** Exercise testing reflect survival in IPF population. Statistically significant correlations were found between survival and CPET parameters such as VO2peak (p=0.02, RR=0.99), VO2peak/kg (p=0.01, R=0.78), 6MWT (p=0.01, RR=0.72), SpO2peak (p=0.01, RR=0.48), VE/VECO2slope (p=0.005, RR=1.09), VE/VCO2AT (p=0.008, RR=1.14) and the 6MWT parameters: distance walked (p=0.008, RR=0.99) and desaturation (p=0.01, RR=1.42).

**Conclusions:** Physiological parameters obtained during maximal and submaximal exercise testing reflect survival in IPF population.

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**P660**

**Proposal for revised classification of disease severity of idiopathic pulmonary fibrosis in Japan**

Hiroyuki Tanaguchi,1 Kensei Katoaka,1 Yasushi Kondoh,1 Sakae Homma,2 Michiaki Mishima,1 Yosikazu Itoue,1 Takashi Ogura,3 Masashi Bando,3 Koichi Hagihara,1 Hiroki Takahashi,1 Kengo Chida,1 Kazuma Kishi3,1 Yukihiko Sugiyama6,1

**Background:** Patients with IPF with acute exacerbations were excluded. Baseline differences in progression covariates or factors were assessed through Mann-Whitney, Chi square or Fisher exact test. Median survival was estimated using Kaplan-Meier method.

**Results:** The comparison between two groups showed lower median values of survival in IPF patients.

**Conclusions:** The Kaplan-Meier survival curve was used to evaluate survival differences between SP and RP. The comparison between the two groups showed lower median values of FVC (60 versus 73) and TLC (57.8 versus 72) and a higher percentage of non-smokers in RP group at time of diagnosis.

**Conclusion:** The analysis of this group of IPF patients confirms two clearly separated phenotypes, SP and RP, that must be discriminated, since they seem to have different presentations and a remarkably different evolution. These results could mean distinct physiopathological pathways, which could implicate different therapeutic approaches.

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**P661**

**Proposal for revised classification of disease severity of idiopathic pulmonary fibrosis in Japan**

Hiroyuki Tanaguchi,1 Kensei Katoaka,1 Yasushi Kondoh,1 Sakae Homma,2 Michiaki Mishima,1 Yosikazu Itoue,1 Takashi Ogura,3 Masashi Bando,3 Koichi Hagihara,1 Hiroki Takahashi,1 Kengo Chida,1 Kazuma Kishi3,1 Yukihiko Sugiyama6,1

**Background:** The aim of the present study was to evaluate the prognostic significance of cardiopulmonary exercise test (CPET) in this group of patients.

**Methods:** Twenty five IPF patients were prospectively recruited and underwent functional evaluation through maximal (CPET) and submaximal exercise testing.

**Results:** Mean survival was 44.4 months.

**Conclusions:** Physiological parameters obtained during maximal and submaximal exercise testing reflect survival in IPF population.
Promising effect of PMX-DHP absorption therapy for acute exacerbation of IPF

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Background: Current agents for the treatment of idiopathic pulmonary fibrosis (IPF) have not been found to improve the prognosis, thus requiring the development of new types of drugs to treat IPF.

Aims: This study was designed to investigate the effect of combination of Salvia (one kind of traditional Chinese medicine) and Ligustrazine (one kind of traditional Chinese medicine) on the expression of inflammatory mediators, the mRNA expression of type I and III collagen, and hydroxyproline content in lung tissues in bleomycin (BLM)-induced rat pulmonary fibrosis.

Methods: Adult Wistar rats were intratracheally instilled with BLM or normal saline (NS). After intratracheal administration, the animals were intraperitoneally injected with combination of Salvia and Ligustrazine or NS every day. Then they were euthanized, and BLM-induced rat pulmonary fibrosis was confirmed. Immunohistochemistry analysis was used to examine the expressions of inflammatory mediators in lung tissues, and the mRNA expression of type I and III collagen and hydroxyproline content in lung tissues was also measured.

Results: Combination of Salvia and Ligustrazine could alleviate alveolitis and fibrosis; could attenuate the expression of inflammatory mediators in lung tissues; and could also decrease the mRNA expression of type I and III collagen and hydroxyproline content in lung tissue in rat pulmonary fibrosis.

Conclusions: Combination of Salvia and Ligustrazine had an anti-fibrosis effect, and it might be considered as a clinically viable option to treat pulmonary fibrosis.
86. Experimental models and research in diffuse parenchymal lung diseases

P666
Late-breaking abstract: Serum and blood cell culture Th17 cytokines in pigeon fencers’ hypersensitivity pneumonitis (HP)

Kenneth Anderson1, Iona Donnelly1, Lisa Jolly1, S. Todryk2, P. Pushparaj2, Kenneth Lipson1, G. Short1, M. Adamson1, Steven Boukhe3, Charles McSharry4, Giuseppe Novelli1, Federica Sangiuolo1.

Methods: Serum cytokines of Th17 production were assessed in 46 pigeon fanciers and 46 controls with no history of HP.

Results: The mean cytokine levels were not different between HP patients and controls, but there was a trend for IL-1b and IL-6 to be higher in HP patients (p=0.066).

Conclusions: The cytokine levels in HP patients were not different from controls, but there is a trend for a higher level of IL-1b and IL-6.

P667
Reduction of lung injury and fibrosis by human embryonic stem cells in a mouse model of silica-induced lung fibrosis

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Methods: We assessed the ability of human embryonic stem cells (HUES-3-ATIICs) to differentiate into functional alveolar type II cells (ATIICs), engraft into damaged lungs and reduce fibroproliferation, thereby reducing mortality, in a mouse model of silica-induced pulmonary inflammation and fibrosis.

Results: We demonstrated that HUES-3-ATIICs could differentiate into ATIICs, engraft into damaged lungs and reduce fibroproliferation, thereby reducing mortality, in a mouse model of silica-induced pulmonary inflammation and fibrosis.

P668
Rapid reversal of radiation-induced murine pneumonitis by treatment with the anti-CTGF monoclonal antibody FG-3019

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Methods: Lung injury was initiated with a single, full thorax irradiation and administration of FG-3019 began 16 weeks after irradiation, when a significant increase in lung density was detectable by computed tomography (CT). Gene expression and histological analysis was performed at 18 weeks after irradiation.

Results: Lung density in placebo-treated mice increased between 12 weeks and 30 weeks after irradiation. Treatment with FG-3019 reversed the radiation-induced lung density increase, which progressively decreased during the 8 weeks of administration and remained constant for another 6 months. Gene expression analysis and histological examination showed considerable infiltration of mast cells and macrophages at 18 weeks after irradiation in placebo-treated animals, while two weeks of FG-3019 restored levels to that of unirradiated mice.

Conclusions: FG-3019 reversed radiation-induced pneumonitis and lung remodeling very quickly after administration was initiated and produced a durable effect on lung density. Because these are key events in the process of fibrosis, the data suggest that inhibition of CTGF can disrupt fibroproliferative processes after they have begun and support continued clinical evaluation of FG-3019 for treatment of pulmonary fibrosis.
**P670**

The stimulator of soluble guanylate cyclase riociguat protects against bleomycin-induced pulmonary fibrosis in mice

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**Background:** Effective therapies for pulmonary fibrosis (PF) are currently lacking. Patients with PF develop pulmonary hypertension (PH), in part due to impaired production of endogenous nitric oxide (NO) that activates soluble guanylate cyclase (sGC). We hypothesized that the NO-independent stimulation of sGC might attenuate PH.

**Methods:** Male C57/BL6 mice (10-12 wks) were subjected to intratracheal attenuation PF. Lung specimens of this model confirmed UIP pattern, such as apoptosis index. We used 5 balb/c mice as controls.

**Results:** Bleomycin-induced PH (an increase in the right ventricle systolic pressure and a decrease in the pulmonary acceleration time/heart rate ratio) and the right ventricular hypertrophy were attenuated by riociguat and the combination of riociguat and sildenafil to a greater extent than by sildenafil alone. In the vehicle-treated mice, fibrosis and inflammation diffusely involved lung parenchyma. Riociguat and its combination with sildenafil but not sildenafil alone markedly ameliorated PH and inflammation that was mainly confined to subpleural areas and/or peripheral lung in a patchy distribution. Riociguat increased plasma cGMP levels and also reduced mortality.

**Conclusions:** Pharmacological stimulation of sGC with riociguat attenuates PF, PH, right ventricular hypertrophy and mortality in the bleomycin-exposed mice. This therapeutic approach appears to be superior to treatment with sildenafil. Stimulation of sGC might represent a new modality for treating PF and related conditions.

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**P671**

Experimental model resembling the histological pattern of usual interstitial pneumonia and reinforcing the epithelial injury as pathway

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The present experimental model in mice was developed to confront the histopathological feature with that of the idiopathic pulmonary fibrosis (IPF) usual interstitial pneumonia (UIP), as we suppose both are caused by the injury of type II pneumocytes (TIIp) and by the increase of collagen system.

**Material and methods:** Twenty male Ibali/c mice are injected ip with 400mg/kg of butylated hydroxyltoluene (BHT) and kept breathing for six days at a 70% oxygen atmosphere. The mice were killed after one month. The lungs were fixed and stained by Hematoxylin & Eosin and immunofluorescence for collagen I and II.Also, TUNEL and electron microscopy were used to evaluate the epithelial apoptosis index. We used 5 balb/c mice as controls.

**Results:** Pulmonary specimens of this model confirmed UIP pattern, such as progressive increase of interstitial deposition. They showed significant increase of collagen I and III deposition and significant increase of epithelial apoptosis when compared to control group (p<0.05). The apoptosis was more prominent in the TIIp observed by electron microscopy.

**Conclusion:** This experimental model showed the same histopathological patterns of UIP, and also reinforced the increase of apoptosis TIIp after injury or apoptosis of these cells and collagen deposition as an early feature in the pathogenesis of IPF. Financial support: FAPESP-CNpq.

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**P672**

Can flaxseed oil reduce experimental lung fibrosis in rats?

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**Background:** The anti-inflammatory effects of polysaturated fatty acids (PUFA) is actually demonstrated. In this study we evaluated protective and therapeutic effects of Flaxseed Oil (FO) on Bleomycin (BLM) lung fibrosis in rats.

**Methods:** 30 males wistar rats were randomly divided into 3 equal groups: untreated group (G1) and 2 treated groups (FO). 1g/kg bw/day). G2 received FO during two months before inducing lung fibrosis than G3 received FO 2 days after inducing lung fibrosis during 10 days. Pulmonary fibrosis was induced by BLM (4 mg/kg, intratracheally single dose). Inflammatory index, fibrosis score (Ashcroft) and TGF-β density was evaluated in different areas of damaged lung by anatomo-histological and immuno-histological analysis.

**Results:** Independent-samplesTtest revealed that comparatively to control group (G1), FO reduced significantly fibrosis score in G2 and TGF-β density in fibrocytes in G3 (p<0.05).

**Conclusion:** These data demonstrated a protective activity of FO against bleomycin-induced lung fibrosis model in rats.

More investigations will be realized in human to prove relationship between diet and interstitial lung diseases.

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**P673**

Inhibition of PAI-1 in the cigarette smoke induced epithelial-mesenchymal transition

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**Introduction:** Plasminogen activator inhibitor-1 (PAI-1) has been known to play an essential role in pulmonary fibrosis by inhibiting plasminogen activator (PA). Recently, it is assumed that epithelial-mesenchymal transition (EMT) play a role in the pathogenesis of IPF. We tried to find out whether PAI-1 is involved in the bleomycin-induced pulmonary fibrosis in the rat and in smoking-induced rat alveolar EMT in vitro.

**Methods:** First, rats were received intratracheal bleomycin (4U/kg) and then administered tiplaxitinin (1mg/kg) at day 1, 3, 5, 7, 10 orally. Rats were sacrificed at day 14. Next, the type II alveolar epithelial cells were isolated from normal rats by percoll gradient methods. Type II epithelial cells were transfected with PAI-1-siRNA and were stimulated with cigarette smoking extract (CSE, 5%).

**Results:** In bleomycin-induced pulmonary fibrosis model, tiplaxitinin decreased the bleomycin-induced pulmonary fibrosis by Ashcroft score and also decreased the PAI-1 and TGF-6 concentrations in the BAL fluids. In epithelial cell experiment, exposure to CSE increased the α-SMA and PAI-1 mRNA expression in real-time PCR. However, they were attenuated either after transfection with siRNA-targeted PAI-1 or treatment with tiplaxitin (50 μM). TGF-6 concentrations in the CSE exposed cell culture supernatants were also decreased either by PAI-1-siRNA transfection or treatment with tiplaxitin. The up-regulation of Smad and pSMAD by smoking exposure in epithelial cells were decreased either by transfection with PAI-1-siRNA or treatment with tiplaxitin.

**Financial support:** FAPESP.
Introduction: Although the etiology of an acute exacerbation of idiopathic pulmonary fibrosis (IPF) is unknown, it may be represented by a clinically occult combination with decreased neutrophils suggests ongoing clearance. Decrease of neutrophils, macrophages and B-cells may suggest migration to lymphoid organs, thus initiation of an adaptive immune response. In summary, we found fibrosis and inflammation occurring in parallel, both present early in the development of pulmonary fibrosis.

Methods: Lung injury was induced in female C57BL/6 mice by the intratracheal injection of BLM. Twenty-eight days after the injection of either BLM or saline, the mice received intratracheal injections of either saline or CpG-ODN. A total number of 4 groups (saline: saline/CpG; BLM/CpG) were investigated. After 24 h, the mice were killed, and the neutrophil counts and cytokine levels were determined in the bronchoalveolar lavage fluid (BALF).

Results: There were no differences in the neutrophil counts between the saline and BLM groups. The neutrophil counts in the BLM/CpG group were significantly higher than those in the saline/CpG group. The levels of macrophage inflammatory protein (MIP)-2 and interleukin (IL)-6 in the BALF were found to be significantly higher in the BLM/CpG group than in the saline/CpG group. Real-time reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemical analysis of the lung tissue revealed an upregulation of TLR9 expression induced by BLM administration.

Conclusion: These results suggest that the TLR9-mediated lung inflammatory responses are enhanced in BLM-induced lung fibrosis in mice.

P675
Enhanced lung inflammatory response to intratracheal CpG-ODN in mice with bleomycin-induced lung fibrosis
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Background: Pulmonary fibrosis is a facet of Diffuse Parenchymal Lung Disease and has been considered a sequel to chronic inflammation. Yet the relation between connective tissue and immune system during the initiation phase has not been thoroughly investigated. Our aim was to investigate the initiation phase and the interplay between immune system and connective tissue.

Methods: C57BL/6 mice were given subcutaneous bleomycin injections (controls received saline) 3 times/week for 1, 2, 3 and 4 weeks. Following sacrifice, lungs were embedded in paraffin and 4 μm thick sections were used for analysis of lung parenchymal Masson Trichrome (total collagen) and immunohistochemistry to detect neutrophils, macrophages and B-cells.

Results: Total collagen was significantly increased at 1, 2 and 4 weeks. A transient neutrophilia was found at 4w (279±820 cells/mm3), but no difference compared to controls was found at 2, 3 and 4w. Macrophages were significantly increased at 2w (135±29 cells/mm3) whereas B-cells were significantly decreased at 3w and 4w compared to controls.

Conclusions: Subcutaneous administration of bleomycin induced rapid pulmonary remodeling, exemplified by increased total collagen. The immune response was markedly different from the one following intratracheal administration, illustrated by the moderate transient neutrophilia. Increased numbers of macrophages at 2w in combination with decreased neutrophils suggests ongoing clearance. Decrease of B-cells may suggest migration to lymphoid organs, thus initiation of an adaptive immune response. In summary, we found fibrosis and inflammation occurring in parallel, both present early in the development of pulmonary fibrosis.

Conclusion: Compared to control groups G3 and G4, ANOVA statistical study, demonstrated that FG Seed Polynexols Extracts ameliorated TASI and reduced inflammatory index and TGF-β1 density in G1 and seeds powder of FG reduced MDA a marker of oxidant stress and inflammatory score in G2 (p < 0.05). However, Ashcroft semi-quantitative assessing of fibrosis score has not revealed significant differences between the four groups (p>0.05).

Conclusion: This study demonstrated that FG 1 has potent antioxidant and anti-inflammatory activities but has not an anti-fibrotic effect confirming that besides inflammation, other factors probably interfere in the pathogenesis of pulmonary fibrosis.

P676
Anti-oxidative and anti-inflammatory effects of trigonella foenum graecum (fenugreek) seed extract in experimental pulmonary fibrosis
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Background: Oxidative stress participated in the pathogenesis of intestinal lung diseases. This prospective study is the first experimental work that evaluated the effect of Fenugreek (FG) and its phenollic extract on oxidative stress and lung fibrosis in experimental model.

Methods: A single dose of Bleomycin was injected intratracheally in forty male wistar rats (45g/kg). Two days after inducing lung injuries, animals were randomly divided in four groups of 10 rats: G1, G2, G3 and G4. G1 received FG Seed Polypenol Extract at a dose of 200 mg kg by daily gavage.G2 received FG seeds powder mixed with food at levels of up to 2%. G3 received an equal volume of water (6.5 ml/kg, daily gavage). G4 did not receive any treatment. Two weeks after inducing lung fibrosis, rats were sacrificed and we evaluated stress biomarkers (TAS:Total Antioxidant Status, Malon DiAldehyde MDA) in serum and inflammatory index, fibrosis score and TGF-β1 density in lung tissue.

Results: There were no differences in the neutrophil counts between the saline and BLM groups. The levels of macrophage inflammatory protein (MIP)-2 and interleukin (IL)-6 in the BALF were found to be significantly higher in the BLM/CpG group than in the saline/CpG group. Real-time reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemical analysis of the lung tissue revealed an upregulation of TLR9 expression induced by BLM administration.

Conclusion: These results suggest that the TLR9-mediated lung inflammatory responses are enhanced in BLM-induced lung fibrosis in mice.

P677
Effect of experimental pulmonary fibrosis induced by bleomycin on the lung fatty acid composition in Wistar rats
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Background: Many recent studies are directed towards the use of natural substances for the treatment of pulmonary fibrosis and of these fatty acids. The main study was first to verify the normal composition of fatty acids in the lungs of rats and collect the effect of experimental fibrosis induced by bleomycin in rats on the latter.

Methods: A total of twenty males wistar rats which received water and food ad libitum, were divided randomly into two groups: untreated group (G1, n=10) and treated group (G2, n=10).

Pulmonary fibrosis was induced in all treated rats (G2) by bleomycin (4 mg/kg, single dose) administered intratracheally. Three day later, all rats were sacrificed, lungs were extracted and blood was collected for analysis of fatty acid composition in the lungs and red cells of rats studied, and this by using the technique of gas chromatography (GC).

Results: The statistical of independent-samples T test revealed that bleomycin alters significantly the composition means of various fatty acids in treated group (G2) compared to untreated group (G1) as shown in the figures below.

Conclusion: These results confirm that bleomycin affects the fatty acid composition of lung giving the opportunity to test the effects of substances rich in fatty acids on pulmonary fibrosis models in rats.
of unknown cause such as idiopathic pulmonary fibrosis. The aim of the current study was to characterize the mechanisms of pulmonary fibrosis and to determine whether IL-17A plays an important regulatory role.

Methods: Balb-BLM (BLM), Balb-Paraquat, C57-BLM and C57-KO IL-17-BLM induced pulmonary fibrosis animal models were used to evaluate the fibrosis and the IL-17 role. We used the picrosirius-polarization method, weigert’s resorcin-fchisin histochemistry, immunohistochemistry, and morphometric analysis to evaluate the amounts of collagen and elastic fibers and the transforming growth factor-β (TGF-β) expression.

Results: Our results indicate that BLM-mediated fibrosis is IL-17 independent, as IL-17-/- mice developed similar amount of fibrosis when compared to control mice. In marked contrast, BLM-induced pulmonary fibrosis revealed increase of collagen fibers in all four groups (Fig 1). We found that only Balb-BLM and Balb-Paraquat presented increase of elastic fibers. A positive correlation was found between elastic and collagen fibers in Balb-BLM animals, as well as in Balb-BLM and Balb-Paraquat. In addition, we found a direct correlation between TGF and collagen in C57-KO-IL-17-BLM.

Conclusions: Bleomycin and paraquat-mediated fibrosis is IL-17 independent. However, more studies are necessary to validate the regulatory role of IL-17 on pulmonary fibrosis process.

P679
The effect of Nigella sativa oil on inflammation, fibrosis and antioxidant enzymes in the bleomycin-induced lung fibrosis model in rats
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The aim of the study was to investigate the effect of N. sativa on bleomycin-induced fibrosis.

All study groups included 8 rats. Intratracheal (IT) saline or N. sativa were given to two control groups. A single dose of IT bleomycin was administered to the bleomycin group (BG) as well as the treatment groups on day 0. N. sativa oil was given by oral gavage between days 0-16 in one treatment group and between days 8-16 in the other. At the end of the study, the lung tissues of all rats were investigated histopathologically; GSH, GSH-Px, SOD enzyme activities as well as collagen and elastic fibers were measured in lung tissues and BAL fluids.

On histologic examination, the ratio of inflammation was observed as 45.6%, 19.3% and 14.1% in the BG, long and short treatment groups, respectively; the difference between treatment arms and BG being statistically significant (p=0.019; p=0.003, respectively). The fibrosis score of the BG, long and short treatment groups were calculated as 1.6, 0.78 and 0.35, the difference being also statistically significant (p=0.004; p=0.0001, respectively).

The IT administration of bleomycin resulted in a statistically significant decrease in the GSH-Px and GSH activities and increase in MDA levels of the lung tissue and BAL fluid in comparison with the control group. The enzyme activities in both groups and BAL samples of both treatment arms were high with respect to the BG, the difference being statistically significant for GSH-Px enzyme activity of the BAL fluid (p<0.01).

Oral administration of N. sativa oil resulted in both a decrease in inflammation-fibrosis and an increase in the antioxidant enzyme activities in the rat model.

P680
Modulation of fibroblast phenotype in idiopathic pulmonary fibrosis: Role of Nrf2
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Rationale: Oxidative stress has been implicated in Idiopathic Pulmonary Fibrosis (IPF) pathophysiology especially in myofibroblastic differentiation. Nrf2 signaling pathway, the main regulator of endogenous antioxidant enzymes, could be involved in fibrogenesis. The aim of our study was to analyze human pulmonary fibroblast expression of Nrf2, and, to assess the effects of Nrf2 modulation on fibroblast phenotype in vitro.

Methods: We assessed antioxidant/antioxidant balance, Nrf2 expression and phenotype of IPF and control fibroblasts in basal conditions, after stimulation by TGF-β, and Nrf2 siRNA transfection.

Results: We showed a decrease of nuclear Nrf2 expression in IPF fibroblasts concomitant with myofibroblast phenotype in basal conditions. TGF-β induced an inhibition of nuclear Nrf2 expression and a myofibroblastic differentiation of control fibroblasts. Nrf2 inhibition in control fibroblast led to an increased oxidative stress in association with a myofibroblastic differentiation. Conversely, Nrf2 activation by Keap1 siRNA, resulted in antioxidant defences restoration and myofibroblastic dedifferentiation in IPF fibroblasts.

Discussion: Our results suggest an association between decreased nuclear Nrf2 expression and myofibroblastic phenotype of IPF fibroblasts. Nrf2 modulation in human lung fibroblasts confirmed the increased susceptibility of Nrf2 knockout mice to bleomycin induced pulmonary fibrosis.

Conclusion: Our study identified Nrf2 as a novel therapeutic target in IPF fibroblasts and suggested a potential anti-fibrotic effects of Nrf2 pharmacological activators.

P681
Serum SP-A and SP-D: Different cutoff values for German and Japanese patients to diagnose idiopathic interstitial pulmonary fibrosis
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Introduction: Surfactant protein (SP)-A and SP-D are members of the C-type lectin superfamily. Serum levels of SP-A and SP-D are known to be elevated in patients with various interstitial lung diseases; however, the majority of these data have been obtained in Japanese patients.

Objectives: This study was conducted to compare serum levels of SP-A and SP-D between the German and Japanese population and to investigate whether SP-A and SP-D could be used as diagnostic biomarkers in German patients with idiopathic interstitial pneumonias (IPDs).

Methods: Serum samples were obtained from Germans (110 patients with IPDs and 57 healthy controls) and Japanese (68 patients with IPDs and 100 healthy controls). Serum SP-A and SP-D levels were measured and cutoff values to discriminate IPD patients from healthy subjects were assessed by receiver operating characteristic (ROC) analysis.

Results: In healthy subjects, serum levels of SP-D were significantly higher in Germans than those in Japanese (63.9±30.4 ng/ml and 40.2±24.4 ng/ml; p<0.001) whereas serum levels of SP-A were not significantly different (32.1±16.9 ng/ml and 27.3±13.3 ng/ml; p=0.100). ROC analysis revealed that the optimal cutoff values to discriminate IPD patients from healthy subjects in Germans and Japanese were 133.5 ng/ml and 103.0 ng/ml for SP-D, and were 38.9 ng/ml and 32.4 ng/ml for SP-D, respectively.

Conclusions: Our data suggest the possibility of SP-A and SP-D to be used as diagnostic biomarkers for IPDs in Germans. Cutoff values to discriminate IPD patients from healthy subjects seem to be different between in Germans and in Japanese, however, further investigations will be required.

P682
LSC 2011 Abstract: Role of mast cells and chymase in idiopathic pulmonary fibrosis
Djuro Kosanovic, Bhola Kumar Dahal, Josef Messinger, Yvan Fischer, Katrin Hoffmann, Jochen Antel, Bettina Huen, Nina Hanke, Stephanie Mayer, Hossein Ardecsch Ghofrani, Norbert Weissmann, Friedrich Grimminger, Werner Seeger, Ralph Theo Schermuly. Medical Clinic II, University of Giessen Lung Centre, Giessen, DE; Abbott Products GmbH, Hannover, DE; Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, DE

Rationale: Mast cell (MC) activation has been implicated in the pathogenesis of inflammatory lung diseases. Among the MC-derived mediators, MC chymase is involved in the processes such as activation of TGF-β and formation of collagen fibrils. The literature suggests that chymase may contribute to the pathogenesis of pulmonary interstitial remodeling; however, a systematic investigation is still missing.

Methods: Lung tissues obtained from donors and patients with idiopathic pulmonary interstitial pneumonias (IIPs). Among the MC-derived activators.

Results: We showed a decrease of nuclear Nrf2 expression in IPF fibroblasts concomitant with myofibroblast phenotype in basal conditions. TGF-β induced an inhibition of nuclear Nrf2 expression and a myofibroblastic differentiation of control fibroblasts. Nrf2 inhibition in control fibroblast led to an increased oxidative stress in association with a myofibroblastic differentiation. Conversely, Nrf2 activation by Keap1 siRNA, resulted in antioxidant defences restoration and myofibroblastic dedifferentiation in IPF fibroblasts.

Discussion: Our results suggest an association between decreased nuclear Nrf2 expression and myofibroblastic phenotype of IPF fibroblasts. Nrf2 modulation in human lung fibroblasts confirmed the increased susceptibility of Nrf2 knockout mice to bleomycin induced pulmonary fibrosis.

Conclusion: Our study identified Nrf2 as a novel therapeutic target in IPF fibroblasts and suggested a potential anti-fibrotic effects of Nrf2 pharmacological activators.
donors. There was a preponderence of perivascular MCs and CMCs in IPF lungs (p<0.05 versus donor lungs). Furthermore, we found that there was about 8 fold decrease of mBorg in IPF patients as compared with donors. Finally, there was a strong accumulation of both MCs and CMCs in interstitial regions of the tissues (~65%) in comparison with other regions of the lungs.

Conclusion: The findings suggest that chymase released from activated MCs may be involved in the pathogenesis of IPF. Further investigations will unravel the underlying pathomechanism and substantiate chymase as a potential target for future therapeutic strategies.

P683

LSC 2011 Abstract: Histological markers of epithelial-mesenchymal transition in idiopathic pulmonary fibrosis provide evidence of an alternative repair process

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Introduction: Wound remodelling in the pathogenesis of idiopathic pulmonary fibrosis (IPF) has produced conflicting results from previous cell culture and animal model studies.

Aim: The aim of this study was to examine wound remodelling mechanisms in usual interstitial pneumonia (UIP), with emphasis on the role of epithelial-mesenchymal transition (EMT).

Methods: Immunohistochemistry was used to assess cellular expressions of markers of EMT in paraffin embedded lung tissue samples from 21 patients with IPF, with comparisons made to histologically-defined normal lung sections from 19 control subjects.

Results: Hyperplastic type II pneumocytes in all UIP cases expressed the adhesion molecule E-cadherin with no expression of N-cadherin or TWIST. Expression of TWIST was restricted to the fibroblast/myofibroblast foci. TGF-β protein was consistently expressed by type II pneumocytes of UIP samples, but to varying degrees within the fibroblastic foci. Collagen I and smooth muscle actin were expressed in the fibroblastic foci.

Conclusions: Myofibroblasts may form a contractile repair response to a micro-injury via secretion of extracellular matrix proteins, providing scaffolding for type II pneumocytes which then divide at the edge of the insult and migrate over the fibroblastic foci surface. TGF-β signalling pathways may lead to the continued accumulation of type I collagen in the foci. Alternatively, abnormal collagen I is produced which is resistant to matrix metalloproteinases inhibiting wound repair. We conclude that tissue remodelling in IPF is a complex process warranting further investigations to fully elucidate the role of EMT in the pathogenesis of IPF.

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The relationship between socioeconomic status, quality of life and healthcare access in COPD: A systematic review

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Introduction: Socioeconomic deprivation is a significant health determinant in COPD. To examine the relationship between socio-economic status (SES), Quality of Life (QoL) and healthcare access in COPD, we conducted a systematic review.

Methods: Medline, Embase, Web of Science, PsycINFO, BIBS, IngentaConnect and CINAHL were searched for quantitative studies published in English (1947-2011). Articles reporting association between SES and any aspect of QoL, and healthcare access were included.

Results: After screening 6889 papers and assessment of 1088 abstracts 76 studies were reviewed. Studies were categorised depending on outcome measures into either quality of life (n=45) or healthcare access (n=31). Quality of life included: disease severity, exacerbations, psychological status, physical functioning/activity, pulmonary function/respiratory symptoms and mobility. 66.7% (n=30) of the studies yielded a negative effect of low SES on QoL, 28.9% (n=13) showed no effect and 4.4% (n=2) found a positive influence. Healthcare access involved: hospitalisation rates, prescription patterns, medication adherence/use and diagnostic procedures. 61.3% (n=19) provided data for the negative influence of socioeconomic deprivation on healthcare access, 29% (n=9) showed no effect while 9.7% (n=3) found a favourable influence.

Conclusion: A consistent association between low SES and unfavourable outcomes in various domains of both QoL, and healthcare access was found. Findings suggest a need to investigate the reasons for this negative association between SES and outcome in COPD. The possible explanatory role of factors such as patients beliefs and behaviour are being explored in an ongoing cohort study.

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The measurement of the impact of breathlessness in advanced COPD

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Introduction: Breathlessness is the main symptom of COPD and should be a key outcome measure in studies of advanced disease. Measures of breathlessness have been poorly researched. There is no gold standard for the assessment of breathlessness in advanced disease. In this study we aimed to identify using existing tools a valid and reliable self-report measure of breathlessness for clinical research in advanced COPD.

Methods: 260 eligible patients with advanced COPD were identified from the disease registers of 72 general practices. Spirometry, MRC dyspnoea scale, mBorg, NRS, CRQ-SAS, Dyspnoea 12, and Hospital Anxiety and Depression Scale, were administered at interview. Distribution of responses, associations and correlations were examined.

Results: 146 (56%) patients were interviewed. Association between the different measures of breathlessness was variable with least correlation between the numerical measures mBorg and NRS and the other measures, and greatest correlation between CRQ-SAS and Dyspnoea 12. Usefulness of tools was limited by ceiling effects (limited room for more severe breathlessness) in MRC Dyspnoea scale and by floor effects (limited room for less severe breathlessness) in mBorg and NRS. Factor analysis of the five measures confirmed that the CRQ-SAS dyspnoea questionnaire (loading 0.74) and Dyspnoea 12 questionnaire (loading 0.73) were closest to the hypothesised latent true value of breathlessness (eigenvalue 2.33, difference 2.21).

Conclusions: Combination of CRQ-SAS dyspnoea and Dyspnoea 12 is the most suitable approach to valid, reliable, measurement of breathlessness in clinical research in advanced COPD that is sensitive to change. mBorg retains a particular role in standardised exercise testing.

P686

Validity of the pediatric electronic quality of life instrument for childhood asthma in the Netherlands

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Introduction: Assessment of health-related quality of life (HRQL) for children with asthma in daily care may facilitate shared decision-making and contribute to patient-centred care. Pediatric HRQL is unique to children and it is essential to establish whether an instrument used in daily care has an individualised part to prioritise issues that are especially important for the particular child. We have developed a pediatric HRQL instrument that is designed as a web based game and has an individualised part (Pelicarn instrument).

Aim: The aim of this study was to determine the cliniometric properties of the Pelicarn instrument.

Methods: 68 children with asthma aged 6 – 12 years were recruited. Children completed the Pelicarn instrument on 3 occasions within a 2-month period. Additional information was collected on various aspects, including asthma control (ACQ, C-ACT) and HRQL (Feeling Thermometer and PAQLQ).

Results: The instrument had good test-retest reliability (ICC 0.83) and internal consistency (Cronbach’s α= 0.90). Moreover, the instrument was able to discriminate between children with controlled and uncontrolled asthma and we observed good correlations with the PAQLQ and Feeling Thermometer (r ≥ 0.6). Finally, the items selected by the children as “worst things about my asthma” (i.e., individualised part) were scored higher by the child than items they did not select (mean difference 0.97; scale 1-5).

Conclusions: The results indicate that the Pelicarn instrument is a valid and reliable instrument. The responsiveness of the instrument needs to be established. Further studies are needed to assess whether implementation of the Pelicarn instrument can facilitate patient-centred care.
Intractable breathlessness in COPD – A suitable case for palliation?

**Aim:** To identify the words most frequently used by physicians and patients to express asthma symptoms and activities limitations caused by asthma.

**P687**

**Introduction:** Breathlessness is the major symptom of concern for people with advanced COPD. Intractable breathlessness may be described as “sustained severe breathlessness in patients who have not obtained relief from conventional treatment”. This study set out to define the prevalence of intractable breathlessness in COPD and potential for its palliation.

**Method:** COPD patient records in south London practices were searched for ≥2 of: FEV1 ≤30% predicted, hospital admissions/exacerbations needing oral steroids, long term O2, and cor pulmonale. Participants were interviewed at home.

Breathlessness was assessed using MRC Dyspnoea Scale, mBorg, NRS, Dypsnoea-12 and Chronic Respiratory Questionnaire. Intractable breathlessness was defined using a combination of FEV1% predicted, CRQ-Dyspnoea, Dypsnoea-12 and the desire for more help. Treatment optimisation was offered where appropriate before reassessment of breathlessness.

**Results:** 5102 patients were identified in 72 practices, 2163 had spirometry-confirmed COPD. 260 (5%) were eligible and 146 (56%) took part. 65% reported breathlessness as their most important problem, 69% reported breathlessness evoking palliative services for these patients is a priority.

**Conclusion:** Intractable breathlessness affects around 1 in 50 COPD patients on 2% of patients with confirmed COPD in the study population.

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**Method:** We conducted a cross-sectional survey of patients with asthma receiving ICS-based treatment for ≥6 months. Participants were interviewed at home and patients/physicians. 63 (43%) were on sub-optimal treatment, 97% of whom received optimisation. Improvements in breathlessness weren’t observed at re-assessment. 29 (20%) participants had intractable breathlessness; an estimated 2% of patients with confirmed COPD in the study population.

**Conclusion:** Intractable breathlessness affects around 1 in 50 COPD patients on 2% of patients with confirmed COPD in the study population.

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**Introduction:** Expression of symptoms and daily activities limitations is a core element in physician-patient dialogue in asthma management. Aim: To identify the words most frequently used by physicians and patients to express asthma symptoms and limitations of daily activities, and to assess the patient-physician concordance regarding these.

**Methods:** The “Asthma Language” study (NCT00986219) (descriptive, cross-sectional survey) enrolled patients with asthma receiving ICS-based treatment for ≥6 months. Interviews and patients chose up to 4 words from 2 lists (a symptoms and a daily activities limitations list) identical for patients/physicians.

**Results:** 695 patients (F 57%, age 46.8±14.8 years) were enrolled. Time since diagnosis was 12.9±9.4 years. Treatment with ICS/LABA±LTRA was reported by 92% of patients. ACQ-5 score was 1.5±1.1. The words most frequently used to express asthma symptoms were “cough”, “dyspnea” and “wheezing” (35-56%), while those used to express activities limitations were “stairs climbing”, “fast walking” and “uphill walking” (40.5%-53%). In terms of word concordance regarding expression of asthma symptoms and activities limitations, full concordance was observed in 43% and 19.1% and partial concordance in 75.4% and 74.9%, respectively. By grouping the words expressing the same symptom, full concordance was observed in 21.7% and partial concordance in 72%.

**Conclusions:** This study showed that there is a discordance regarding physician-patient communication in terms of the words used to express symptoms and daily activities limitations caused by asthma.

**P690**

**Facilitation of optimal asthma management to radically influence health policy in primary care in Ireland**

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Prior to the initiation of this program guideline based care was not prioritised by health policy. Asthma control is sub-optimal in Ireland; recent primary care data shows 14% of asthma patients attended A&E, 8% hospitalised in the previous 12 months.

**The Asthma Society of Ireland (ASI) developed a framework for the Dept. of Health and Health Service Executive (HSE) in collaboration with Healthcare Professional (HCP) bodies based on nationally modified guidelines (GINA) and a core program to assess the feasibility of implementing a National Asthma Program.** The ASI funded and developed an asthma management program in primary care to identify barriers and facilitators to implementation of guideline based care. 25 primary care teams completed a guideline based educational program and practical training session. Each team was given a tool-kit with spirometer, peak flow meters and diaries, patient education materials, placebo inhalers and spacers. Adherence to guidelines was facilitated with a specifically developed Electronic Patient Record. 778 patients were included in the program for 6 months.

**A guideline based asthma program can be implemented successfully if practices are provided with necessary resources for diagnosis, management and patient education.** HCP agreed guidelines improved patient care (92.7%), facilitated cost effective care (70.7%). Arising from this study HSE has prioritised the development of a National Asthma Program with asthma specific key performance indicators in its service plans. Active collaboration between patient organisations, HCP and health service providers has lead to a fundamental change in asthma health policy in primary care.
Introduction: A previous survey highlighted a very high degree of physiologically unnecessary home oxygen use in COPD patients (Bhattacharya M, Potter A, Mukherjee R. Assessing for Long Term Oxygen Therapy (LTOT) in an English town. Ann R Coll Surg Eng 2008;87:466). A common reason for the unnecessary use is that hospital physicians discharge COPD patients with home oxygen pending physiological assessment in the hope of preventing future hospital admissions, which we set out to examine.

Methods: A retrospective review of COPD admissions and re-admissions of Birming ham East and North Primary Care Trust from patients from April 2007 - November 2010 based on International Classification of Diseases coding (ICD); Wclie’s 2-sample t-test was applied to assess the significance of the difference in the admission rates of the 2 groups of COPD patients who receive and did not receive LTOT on discharge.

Results: A total of 1942 patients were eligible of which 295 received LTOT on discharge. The mean annual admission rate in the LTOT group was 3.18 and 1.67 in the other (p < 0.0000000001).

LTOT prescription on discharge

<table>
<thead>
<tr>
<th>No of patients</th>
<th>LTOT prescribed</th>
<th>No LTOT prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>295</td>
<td>1647</td>
<td>1329</td>
</tr>
</tbody>
</table>

No of episodes 937 2745

Mean number of episodes per patients 1.58 1.67

Mean ACQ and CCQ scores in these patients according to the level of control are as follows.}

Mean ACQ and CCQ scores for diagnosis selected by ACQ cut-off values

<table>
<thead>
<tr>
<th>ACQ Cut-off</th>
<th>Diagnosis</th>
<th>ACQ average</th>
<th>CCQ average</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.75</td>
<td>COPD</td>
<td>0.31</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>0.32</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Asthma/COPD</td>
<td>0.35</td>
<td>0.66</td>
</tr>
<tr>
<td>0.75–1.50</td>
<td>COPD</td>
<td>1.07</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>1.08</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>Asthma/COPD</td>
<td>0.87</td>
<td>1.28</td>
</tr>
<tr>
<td>&gt;1.50</td>
<td>COPD</td>
<td>2.17</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>2.23</td>
<td>2.25</td>
</tr>
<tr>
<td></td>
<td>Asthma/COPD</td>
<td>2.26</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Conclusion: LTOT prescription on discharge is actually associated with a significant increase in re-admission to hospital of COPD patients. Further studies including controlling the admission rate for disease severity are necessary. Continu ing to widen the provision of integrated multidisciplinary oxygen assessment services also seems to be reasonable.

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Body mass index and quality of life in patients with asthma

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Background: We examined the effect of overweight and obesity on quality of life in patients with asthma.

Methods: Two hundred out-patients with asthma (aged 18 - 80 yrs, mean age 55 yrs, 33% males) were divided into 3 groups: with normal body mass index (BMI<25), overweight (25≤BMI<30) and obese (BMI≥30). Quality of life was measured by using Russian version of St.George’s Respiratory Questionnaire (SGRQ).

Results: Fifty eight percent of males and in 69% of females with asthma had BMI<25: 35% of males and females were overweight and 23% males and 34% females were obese. BMI in males was 26.8±0.62, in females – 28.9±0.55 (p<0.05). Correlation of age and BMI was significant only in males (r=0.35, p<0.05). The relationship between BMI and Symptom score was not determined. BMI in pa tients with asthma was mainly associated with Activity score (r=-0.22, p<0.05), in both males (r=-0.27, p<0.05) and in females (r=-0.22, p<0.05), with Impact (r=-0.17, p<0.05) and Total score (r=-0.09, p<0.05). In patients with BMI<25 and in those with BMI≥25 the differences of Activity (39.7±3.38 vs 49.3±6.7, p<0.01) and Impact scores (29.9±2.64 vs 36.9±1.82, p<0.05) were significant. We did not reveal any relationship between normal BMI and SGRQ scores in pa tients with asthma. Overweight and obesity were associated with Activity (r=0.20, p<0.05) and Total score (r=0.17, p<0.05). In asthmatic males the relationship between BMI≥25 and SGRQ Activity score was (r=0.41, p<0.05), Impact score (r=0.33, p<0.05) and Total score (r=0.37, p<0.05) were determined.

Conclusion: Obesity and overweight are frequently associated with asthma. There was a significant correlation between BMI≥25 and Activity, Impact and Total items of SGRQ.

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Relation between quality of life and morbidity and mortality in COPD patients: 7-year follow-up study

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In this study, relationship between pulmonary function test (PFT) and quality of life (QoL) and effect of QoL on prognosis, mortality, and morbidity were investigated in patients with COPD.
In this prospective study, 251 patients with COPD as defined by ATS criteria were included. 218 patients (86.85%) were male and mean age was 65.55. PFT and QoL questionnaires, St. George Respiratory Questionnaire (SGRQ), were performed at the beginning. During 7 year follow-up, first exacerbation day, number of exacerbation, number and duration of hospitalization, number and duration of hospitalization in intensive care unit, number of readmissions, and exitus day were recorded. 195 patients (77.6%) were died during follow-up. 112 patients (57%) were died due to respiratory reasons. When the beginning parameters of dead patients and survived patients were compared, there was a statistically difference according to comorbidity especially cardiac disease, disease duration, PFT parameters, and SGRQ score (p<0.05). Also number of exacerbation before study and first exacerbation day during study were related with mortality (p<0.05). When the correlation between FEV₁ values, SGRQ scores and parameters mentioned above were investigated, there was significant correlation between these parameters and this correlation was more significant in SGRQ scores than FEV₁ values.

As a result, not only PFT but also quality of life questionnaires are useful in determining the prognosis of COPD, for this reason health questionnaires provide a valid and standardised estimate of the overall impact of COPD and should be used to complement spirometric measurements of baseline assessment of patients in routine practice.

**P696**

**The impact of “specialized COPD outpatient clinic” in patient outcomes – A prospective cohort study in a Hong Kong government hospital**

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**Introduction:** A highly specialized COPD outpatient clinic, run by respiratory specialists, can provide comprehensive and updated service to COPD patients and may reduce their exacerbation/hospitalization rate.

**Aim:** To evaluate the impact of “specialized COPD clinic” on various patient outcomes.

**Methods:** Patients with spirometry-confirmed COPD and history of at least one episode of exacerbation in past one year were referred to the new specialized clinic. GOLD guideline was strictly adhered. Education was provided by respiratory nurses with provision of written action plan for exacerbation of symptoms. Outreach physiotherapy was provided for selected patients. Outcome measures included lung function test, St George respiratory questionnaire (SGRQ), were done at baseline and 6-month follow up. The exacerbation and admission rate were also recorded.

**Results:** Total, 117 patients had been followed up. They had a mean age of 70.34±5.56 (Median 70.5) (range 59-80); SGRQ score total score was 41.4±18.9 and a baseline exacerbation and admission rate 3.3±0.3 and 1.4±1.7 per year respectively in past one year.

At 6-month follow up, patients’ quality of life improved significantly with SGRQ total score reduced from 35.6±18.9 to 28.4±16.6 (RMANOVA test, p=0.018). There was also a 66% reduction in both exacerbation and admission rate. The exacerbation rate reduced from 3.3 to 1 episode/year (0.79 episode per 9 months) while the admission rate decreased from 1.4 to 0.37 episodes/year (0.35 episode per 9 months).

**Conclusion:** The specialized COPD clinic significantly reduces exacerbation and admission rate in COPD patients as well as improves their quality of life.

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**The percentage of influenza vaccination in urban and suburban high risk population in western Greece during the year 2010**

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**Aim:** To estimate the percentage of immunization against influenza.

**Method:** 1156 high risk patients were asked for having or not having done the influenza vaccine. They were also asked for the reasons which made them not to be vaccinated.

**Results:** 227 patients (35.1%) from the rural and suburban were vaccinated and 133 (26.1%) from the urban.

The reasons for no vaccination were fear, ignorance, personal beliefs, neglect, contraindications and lack of vaccine or difficulty in access.

The vaccination was carried out by family physicians in 65.6% of the rural and suburban population and in a 53.4% of the urban.

**Conclusion:** People from rural and suburban areas are more immunized against influenza compared with those from urban. Apart from the contra-indications, there are other reasons that influence the influenza vaccination of the population. The participation of the family physicians in rural population’s vaccination indicates the quality of the direct relationship between doctor and patients and probably is the main cause for the low percentages of fear, ignorance or neglect about the vaccine against influenza.

**P698**

**Influenza vaccination programme – Are the UK government incentives working?**

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**Background:** Influenza A (H1N1) virus has spread globally in recent years. The UK government recommends all people in high-risk groups (all >65 yrs old, people with chronic diseases, the immunocompromised, carers, healthcare workers & pregnant women) be vaccinated against H1N1. Pregnant women are four times more likely to be hospitalised due to the virus as compared with non-pregnant women [1]. The rate of H1N1 hospitalisation among children is also significantly higher compared to those over 65 years old [2]. General practices in the UK are given financial incentive to achieve >70% uptake in high-risk groups.

**Methods:** We retrospectively reviewed vaccination uptake amongst the high-risk population in two practices in different regions of the UK for winter 2010/11. Both practices use the computer input software (EMIS). The programme Population Manger was used to retrieve the uptake data.

**Results:** Both surgeries are achieving the required national target, practice A: 75% (1502/1998) & practice B: 81% (917/1250), hence received full financial incentive. However, both practices have a very low uptake in under 16 year olds, practice A: 35% (277/787) & practice B: 40% (215/522) and among pregnant women, practice A: 40% (12/30) & practice B: 14% (4/28).

**Conclusion:** Incentives for the vaccination programme should be revisited so that all the sub groups of high-risk population, including those most at risk of complications and hospital admissions, achieve the same high level of immunisation.

**References:**


**P699**

**Asthma control and quality of life: 6-month follow-up of PRISMA study (PRospective Study on asthMA control)**

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**Rationale:** According to GINA guidelines, asthma control is the goal of the treatment.

**Objectives:** To estimate the percentage of controlled asthmatic patients and their quality of life.

**Method:** Adult asthmatics with not well controlled asthma (Asthma Control Test score ≤ 19) were involved in a prospective observational study. Asthma control and quality of life were assessed with ACT and EuroQol-5D, respectively.

**Results:** 735 patients were evaluated. Figure 1 shows the distribution of asthma control and quality of life over the 6-month follow-up period.
control at enrolment visit and after 6 months. As compared to the first visit, 70.1% of uncontrolled and 80.0% of partly controlled reached asthma control. The mean (SD) of EuroQoL score was 0.72 (0.2) at first visit and 0.84 (0.2) at 6-month follow-up visit. The mean (SD) of VAS was 65.0 (16.1) at first visit and 77.1 (13.6) after 6 months. Figure 2 shows the EuroQoL score and VAS stratified for control level.

Conclusions: Improvements in asthma control and quality of life can be detected in the majority of non-controlled patients after 6-month follow-up in a real life setting.

P700
Impact of therapy reviews in real-world asthma
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Rationale: Asthma therapy reviews aim to regain or improve asthma control, reduce side-effects and/or contain costs. Little work has been done using clinical data to evaluate their effect on asthma control. Objective: Identify therapy reviews in fixed-dose combination inhaled corticosteroid/long-acting beta2 agonist (FDC ICS/LABA) asthma patients and evaluate subsequent changes in asthma control.

Method: Utilised the UK’s Optimum Patient Care Research Database to identify primary care patients (18–80yrs) with asthma (diagnostic code and/or ICD-10 code) treated with FDC ICS/LABA who, following a therapy review, were prescribed beclometasone dipropionate/formoterol (BDP/FOR; Foster 100/6µg) at same or lower BDP-equivalent ICS daily dose as their previous ICS/LABA. Proxy asthma control measures were evaluated before (over 1yr) and after (≥90 days follow-up) initiating BDP/FOR, i.e. asthma control: no hospital attendance, admissions, or out of hours consultation, outpatient department attendance or admission for asthma; no acute oral steroid prescriptions; no primary care consultations for lower respiratory tract infection, short-acting beta2 agonist (SABA) use, and exacerbations: asthma hospital attendance or Accident & Emergency admission and/or acute oral steroid courses.

Results: 65 eligible patients.

<table>
<thead>
<tr>
<th>Achieved control</th>
<th>Before, n (%)</th>
<th>After*, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SABA µg/d</td>
<td>45 (69)</td>
<td>48 (74)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0</td>
<td>42 (65)</td>
</tr>
<tr>
<td>≥1</td>
<td>1–199</td>
<td>8 (14)</td>
</tr>
<tr>
<td>≥200</td>
<td>16 (22)</td>
<td>17 (26)</td>
</tr>
</tbody>
</table>

*Annually for <1yr outcome; p=0.05 for all measures.

Conclusion: These preliminary data suggest initiating BDP/FOR in real-world FDC ICS/LABA patients following a therapy review does not result in a deterioration in asthma control measures.

P701
Evaluation of COPD treatment success by office-based pneumologists in Germany using the example of tiotropium
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Background: In chronic obstructive pulmonary disease (COPD) patients, treatment with the long-acting anticholinergic tiotropium has been associated with clinical benefits in patients.

Aims and objectives: To assess the treatment effect of tiotropium and evaluate the two most important therapeutic outcome parameters from the perspective of office-based pneumologists in Germany.

Methods: Patients received tiotropium (SPIRIVA® HandiHaler® 18 µg or SPIRIVA® Respimat® 5 µg qd) for 6 to 12 weeks in an open-label observational study in 277 pneumology practices. At Visit 2 (Week 6 to 12) pneumologists assessed the success of treatment with tiotropium and determined the two most important outcome parameters for their judgement of therapeutic success. Other endpoints were the concurrent proportion of positive efficacy and tolerability assessments by both physicians and patients.

Results: Of 1264 patients enrolled, 1264 (100%) were evaluable for the primary efficacy endpoint (mean age, 65.3 years; 63.1% men). Rate of therapeutic success was 96.4% (95% confidence interval [CI]: 95.3-97.4%). The most frequently used specific outcome parameters were pulmonary function (49.1%) and exercise capacity (48.9%). Concurrent proportions of positive assessments by both physicians and patients were 88.4% (95% CI: 86.5-90.1%) and 93.4% (95% CI: 91.9-94.7%) with regards to efficacy and tolerability, respectively.

Conclusion: A high proportion of office-based pneumologists rated the treatment with tiotropium as successful based mainly on improvements of pulmonary function and exercise capacity.

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88. New mechanisms in airway disease

P702
microRNA regulation of the Alpha-1 antitrypsin gene
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Introduction: Alpha-1 antitrypsin (AAT) deficiency is a conformational disorder characterised by chronic inflammatory lung disease and liver disease. microRNAs (miRNA) represent drug targets that function as post-transcriptional negative regulatory molecules of target gene expression. Aims and Methods: To identify miRNAs that target AAT gene expression using in silico analysis, to quantify AAT gene and protein expression in monocytic THP-1, 16HBE14o- bronchial epithelial and HepG2 liver cells using qRT-PCR and ELISA, to quantify specific miRNAs expression in these cells, to modulate AAT expression using pre-miRs and to validate miRNAs targeting AAT using AAT-3’UTR luciferase reporter plasmid in HEK293 cells.

Results: In silico analysis predicts multiple miRNAs that target the AAT gene such as miR-940 (with multiple binding sites in the 3’UTR), miR-132 and -212. Diverse AAT expression using premiRs and to validate miRNAs targeting AAT using a AAT-3’UTR luciferase reporter plasmid in HEK293 cells. A combination of pre-miRs over-expressed in HepG2 only resulted in a decrease of AAT mRNA and protein expression involving premiR-940, however, not significantly more than cells transfected with premiR-940 alone.

Conclusion: AAT mRNA is a true target for miR-940, 132 and 212. miR-940 is a more effective inhibitor than miR-132 or miR-212 due to attractive inherent properties compared to the other miRNAs tested.
P703
Inflammatory mediators in COPD patients with and without alpha-1-antitrypsin deficiency
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Introduction: Systemic inflammation is present in a large proportion of COPD patients and is discussed to be the missing link between COPD and its extrapulmonary manifestations. Little is known about differences in systemic inflammation in COPD patients with and without alpha-1-antitrypsin deficiency (AATD).

Aims: We tested the hypothesis that systemic inflammation in COPD would differ in patients with and without AATD and that markers of inflammation would be associated with quality of life (QoL).

Methods: In this cross-sectional study we included 102 participants. We measured lung function, quality of life (QoL) using the St. Georges Respiratory Questionnaire (SGRQ), and inflammatory mediators in peripheral blood. We compared combined genotype frequencies in four groups: AATD patients without augmentation therapy (AATDunsub = 20); AATD patients with augmentation therapy (AATDsub = 20); patients with COPD (n=46) and healthy controls (HC; n=16).

Results: Geometric mean high sensitivity C-reactive protein (hsCRP) was significantly elevated in COPD (3.72 mg/l) and AATDsub (4.19 mg/l) compared to AATDunsub (0.96 mg/l) and HC (0.82 mg/l). Significant differences could also be detected for alpha-1-antitrypsin (<0.001). Interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha did not differ significantly. hsCRP levels were positively correlated with SGRQ in COPD patients without AATD (Spearman’s r=0.46; p<0.05).

Conclusion: Low grade systemic inflammation is present in COPD with and without AATD. Despite different causes of these diseases, a common inflammatory pathway may exist. In patients with COPD, but not in AATD patients, systemic inflammation is associated with QoL.

P704
Polymorphism of collagen I gene and glutathione-S-transferases T1 and M1 in chronic obstructive pulmonary disease associated with cardiovascular disease
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The aim of the research was to establish association between presence of mutant genotype COL1A1 (locus G1546T), null- genotypes of glutathione-S-transferases (GSTs) GSTM1 and GSTT1 and stage of chronic obstructive pulmonary disease (COPD). The group of patients with COPD (II and III stage of COPD, n=30) associated with I-II functional groups of stable stenocardia (I and II subgroup, n=30) was examined.

In the research of gene COL1A1 polymorphism allelic phenotype T was found in 15% of healthy persons. Genotype GT was revealed at 1/3 of control group while pathological homogeneous genotype TT in the same group hadn’t been registered. In both groups frequency of genotype GT was higher than in the control group (1/3 vs. 0.05, p<0.01). Genotype TT was found in II group only (1/3 vs. 0.05, p<0.01). The OR of severe COPD in the presence of pathological allele T of COL1A1 was especially higher in II group, than in I (OR=1.75, 95% CI=1.11-2.76, p=0.01). Patients with pathological genotype of COL1A1 had been screened for the presence of combined null- genotype of GSTs. The homozygous deletion of both genes was found at four patients (all patients from II group). Respectively those patients had pathological genotype GT of COL1A1 demonstrated by functional inadequacy of collagen 1A1. Presence of combined null-genotype GSTM1 and GSTT1 at these patients, in turn, can lead to the total absence of enzymes GSTs, contributing accumulation of toxic intermediate metabolites of xenobiotics in the cell without their further neutralization and development of oxidative stress and destruction of connective tissue.

P705
Sputum biomarkers in stable COPD
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Characterization of the COPD proteome could help early diagnosis of the disease and aid the development of specific treatment options. The aim of this study was to detect sputum biomarkers characteristic for COPD. Induced sputum was collected from 19 stable COPD patients (GOLD I-II, ex-smokers, mean age 62 years, pack year 52, FEV1 64% predicted, FVC 50%) and 19 healthy controls (mean age 62 years, pack year 29, FEV1 110% predicted, FVC 7%). CRP level, 9.1mg/L vs. 5.1mg/L, and total sputum cell number (3.5×10⁶ vs. 1.3×10⁶) were significantly different between the two groups. Sputum supernatants were subjected to cytokine antibody microarray analysis. Of the 120 cytokines investigated 96 was detectable above background level in 19 majority samples. A greater subset of factors was down regulated while a smaller subset was up regulated in COPD. 14 cytokines exhibited a difference of at least 50% in relative expression level. IL-6, IL-1α, GRO and GROα expression was significantly different (p<0.05) in COPD patients vs. healthy controls. These results suggest that a COPD specific cytokine pattern might exist.

P706
Polymorphism of glutathione-S-transferases T1 and M1 in chronic obstructive pulmonary disease
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Chronic obstructive pulmonary disease (COPD) is the result of genetic factors and environmental conditions influence on a human organism. Glutation-S-transferases (GST) play significant role in cell resistance to oxidative stress, and in prevention of DNA damage from products of tobacco smoke. In this study it was investigated the presence of combined null-genotype of GSTs. The homozygous deletion of both GSTM1 and GSTT1 at these patients, in turn, can lead to the total absence of enzymes GSTs, contributing accumulation of toxic intermediate metabolites of xenobiotics in the cell without their further neutralization and development of oxidative stress and destruction of connective tissue.

P707
Gene regulation of apoptosis and telomere length in COPD and lung cancer
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The aim of this study was to investigate the role of gene regulation of apoptosis (TP53, TP53 I3, FASLG, BAX, CCND1) and telomere function (TRF1, TRF2) in peripheral blood lymphocytes in COPD and lung cancer.

Methods: Groups included 16 COPD patients (FEV1 41-64), 5 lung cancer and 12 controls. Relative telomere length and apoptosis in peripheral blood cells were analyzed by flow cytometry. Relative quantification (RQ) of gene expression was investigated by the RT-PCR System and TaqMan technology.

Results: In COPD a decreased RQ was shown for FASLG, TP53 and TP53 I3 genes with overexpression of BAX (p<0.001) and CCND1 genes and increased expression of BAX-protein and MAPK14 (p<0.05) on CD16+56+ cells by flow cytometry. A significant decrease was demonstrated TERF1 and especially TRF2 expression (Fig. 1). In lung cancer high Ki-67+ and HER2+ cell counts were combined with a decrease of BIRC5 and FASLG expression and MAD2, MAPK14 and CDKNI1B over-expression. The RTL was higher in lung cancer as comparing with COPD and control but no correlation was seen with TERT or TRF2 gene expression.
Peripheral insulin resistance accounts for impaired glucose tolerance and is associated with systemic inflammation in COPD

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Introduction: Impaired glucose tolerance is common in COPD (Archer & Baker, Resp Med: COPD Update 2009:5:67-74). We assessed pancreatic function, hepatic and peripheral insulin resistance and determined the relationship of these with systemic inflammation.

Methods: Participants were 8 stable COPD patients (C) (4 male, 66±8 yrs, FEV1 44.4±16预/秒), predomediated body mass index (BMI) 23±6kg/m2) and 8 healthy volunteers (V) (8m, 24±5yrs, FEV1 89.1±24预/秒, BMI 22±2.5kg/m2) without diabetes mellitus and with fasting glucose <7mm. Participants underwent 120min oral glucose tolerance testing (OGTT). Hepatic insulin resistance (HOMA-IR) and pancreatic beta-cell function (HOMA2-%B) were derived from fasting values and the Matsuda Index (composite hepatic and muscle insulin sensitivity) from OGTT values.

Results: Fasting glucose (p=0.038), Hba1c (p=0.013) and C peptide (p=0.028) were higher in COPD than in volunteers, but insulin was not different (p=0.234). HOMA2 IR was: C 1.3 [0.8-1.8], V 1.0 [0.7-1.2], p=0.161, Matsuda Index was: C 3 [3-5], V (8-6-10), p=0.002. In COPD, but not volunteers, ln(CRP) was inversely correlated with ln(Matsuda) (R=0.76), p=0.047 but not with other homeostatic measures after controlling for BMI.

Conclusion: Non-obese COPD patients without diabetes had increased composite, but not hepatic, insulin resistance compared to volunteers, indicating skeletal muscle insulin resistance. Possible mechanisms underlying the correlation between peripheral insulin resistance and inflammation include inhibition of insulin receptor signalling by inflammatory mediators or pro-inflammatory effects of elevated glucose.

P709 MKK3 is expressed in cells from patients with allergic asthma

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MKK3 is a member of the J38 MAPK signalling pathway. Studies have shown that MKK3 is an important factor in non-allergic inflammatory and Th1 responses. Less is known about its role in allergic inflammation and allergic disease. Proteomic analysis was performed on peripheral blood cells obtained from 22 healthy and 18 allergic asthmatic patients. Lysates from purified lymphocytes were separated by SDS-PAGE and the protein inventories of each sample were identified using mass spectrometry. A 3.65 fold increase in the expression of MKK3 was observed in CD8+ T lymphocytes from asthmatic in relation to healthy volunteers, (% vol protein abundance). Western blot (WB) analysis showed MKK3 expression in lung CD4+ lymphocytes, human endothelial cells (HEVECs) and human epithelial cells (HBEct) but not in neutrophils or eosinophils. However, using densitometric analysis we found no differences between healthy and asthmatic subjects (%vol=10) in any of the cell types analysed. Real time PCR studies showed no expression of MKK3 isoform C in any tissue or cell type. However, large quantities of isoform B gene expression were found in neutrophils and lung tissue from patients with COPD (isoform A: 450 vs Isoform B: 1500 relative expression (ACT-)). MKK3 expression was also measured in lung samples from mice treated with lipopolysaccharide (LPS) or saline. Densitometric analysis of WB data showed that LPS treated mice developed an increased total MKK3 protein expression compared to saline-treated mice (sham: 49 vs LPS: 60 A U, p=0.05). No significant increase in expression in these tissues was observed in mice allergic to ovalbumin. In conclusion, MKK3 is differentially expressed under non-allergic and allergic conditions.

P710 Airflow inflammation and airway pathophysiology in older asthmatics

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Background: Asthma morbidity increases with ageing, which may partially result from alterations in airway pathophysiology. We aimed to describe determinants of ventilatory function and airway responses in older asthmatics to further our understanding of pathophysiological mechanisms.

Methods: Bronchial constriction was induced with hypertonic saline (HTS) in 30 asthmatics aged over 54 years (75% female). The response dose ratio (RDR,%change/mg saline) was used to quantify challenge response: RDR-FEV1/FVC reflecting airway narrowing, and RDRFVC reflecting airway closure. These measures were regressed against markers of airway inflammation (Induced sputum (+) neutrophils and eosinophils and exhaled NO).

Results: Average (SD) FEV1 was 78%pred (16), FVC 91% (12) with 13% (9) fall in FEV1 during HTS challenge. Baseline ventilatory function was inversely correlated with s-neutrophils (r=0.61, p=0.53 and r=0.56 for FEV1%, FVC% and FEF25-75/FVC respectively, all p<0.05), as well as sputum markers of neutrophils (neutrophil elastase, IL-8 and MMP), but not s-eosinophils (p=0.05 for all).

In contrast, the challenge response was predicted by eNO (RDRFEV1/FVC: r= -0.42, p=0.05), indicating airway narrowing associated with airway inflammation. Age predicted an increased RDRFVC (r=0.47, p=0.02), suggesting an increasing tendency to airway closure with ageing.

Conclusions: In older asthmatics, the pattern of inflammation bears important relationships to airway physiology. Neutrophilic inflammation is an important determinant of baseline ventilatory function, whereas airway reactivity relates to eosinophilic inflammation. Age is also determinant of airway closure, consistent with an age-related reduction in parenchymal airway support.
PT13 GATA-3 or T-bet: Who is the crucial marker of allergic bronchial asthma
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The aim: to establish features of expression of GATA-3 and T-bet in bronchial asthma (BA).

Material and methods: 20 healthy, 44 patients with allergic and 42 with non-allergic asthma were examined.

Transcription factors GATA-3 and T-bet expressed in peripheral lymphocytes were analyzed by Western blot after cells were lysed. Preparation of lysates, and the Western blotting were performed through standard procedure. Antibodies against GATA-3 (Abcam, UK), T-bet (Santa Cruz Biotechnology) were used. Level of protein analyzed according to β-actin using anti-actin antibody (Sigma Aldrich, USA).

Results: Expression of GATA-3 was significantly increased and expression of T-bet was significantly decreased in lymphocytes of patients with allergic BA compared to healthy (p<0.04) and non-allergic BA groups (p<0.005). The level of GATA-3 in allergic BA negatively correlated with the degree of airflow obstruction (r = 0.4, p<0.01; n=41) and positively correlated with intensity of steroid therapy (r = 0.33, p<0.03; n=42). The level of T-bet in non-allergic BA positively correlated with the prevalence of asthma triad (r = 0.4, p=0.01; n=42) and drug intolerance (r = 0.43, p<0.005; n=42).

Conclusion: GATA-3 and T-bet may play a key role in the pathophysiology of BA. The expression of GATA-3 and T-bet may serve as markers of allergic BA to provide necessary dose of steroids in patients with BA. This study suggests that allergic BA underlie the high level of Th2-cytokines production in allergic disease.

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Research grant of the year” for the best scientific work.

PT14 Expression of CD38 and its participation in formation of endothelial dysfunction in patients with bronchial asthma
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In the article we studied the role of CD38/ADP-ribosilcyclase in formation of endothelial dysfunction in patients with bronchial asthma.

In the research we have included patients with mild (1st group) and severe (2nd group) bronchial asthma. We found the increased expression of CD38 in peripheral blood lymphocytes in patients of both groups (in the 1st group 4 out of 300 cells, in the 2nd group 6 out of 300 cells) in an exacerbation in comparison with the control group (2 out of 300 cells). Increase of level of expression CD38 promotes the realization of the mechanism of interaction of the activated lymphocytes with the cells of endothelium expressing of non-subtracted lipid CD38 – CD31/PECAM-1.

We note increase of sPECAM-1 in plasma of peripheral blood in the 2nd group to 7.19 ng/ml [6.8, 7.7] in comparison with results of the patients of the 1st group: 6.76 ng/ml [6.1, 7.4]. The increase of expression of sPECAM-1 is significantly different (p=0.025292).

We found the positive interrelation between the level of CD31 and the expression of CD38 (r=0.3; p<0.05), and also direct correlation relationship between the level of CD31 and the concentration of C-reactive protein in blood plasma (r=0.39, p<0.01). The result of such relationship is the damage of cells of endothelium and formation of endothelial dysfunction which, in its turn, determines the disturbance of mechanisms of endothelial regulation of vascular wall elasticity and increase of its rigidity.

PT15 The role of genetic polymorphism of NO-synthase in the implementation of the “atopic march”
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NO-synthase genes are candidate for development bronchial asthma (BA) and atopic dermatitis (AD), because nitric oxide and its metabolites are involved in the formation of oxidative stress and nitrolyzing. We planned and conducted study of genetic polymorphisms of NO-synthase genes associated with clinical and functional manifestations of bronchial asthma and atopic dermatitis for the formation of molecular predictors of implementation of the “atopic march”.

Materials and methods: Material study were DNA samples of patients with asthma (n = 929), BA (n = 847), AD + BA (n = 460). As a control, the DNA of healthy subjects (n = 720).

Results: Established genotypes increase the risk of formation of “atopic march”: TT genotype polymorphism 276 CT, AC polymorphism 186 A/G gene nNOS (RR = 4.56, p = 0.003); 220/220 polymorphism (TAA/A) n, GC and CC polymorphism 954G/C, s/s on the number of repeats (CTTCT) n gene iNOS (RR = 1.60, p = 0.002); polymorphism VNTR, CG polymorphism 894G/C gene of eNOS (RR = 3.75, p = 0.001).

Found haplotypes of genes involved in the implementation of the “atopic march’’atopic march”: (nNOS, iNOS, eNOS): T276 (276CT, nNOS) + C186 (-186A/C, nNOS)+ G (954CTT) n, nNOS + G954 (954GC, iNOS) + 220 (TAA/A) n, iNOS + G989 (989AG, eNOS)+ a (VNTR), eNOS.

PT16 The influence of cigarette smoke on the polymorphism of matrix metalloproteinase (MMP2) in asthmatic patients
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Introduction: Matrix metalloproteinases (MMPs) are a large family of proteolytic enzymes that degrade the components of extracellular matrix (ECM) and MMPs are involved in the pathogenesis of both chronic lung disease: asthma and COPD.

However, its role is not clear.

Aim of this study: to determine whether cigarette smoke plays a role in induction of polymorphism of MMP-2 in tunisian patients.

Patients and methods: A total of 150 asthmatic patients (36 smokers and 114 non-smokers) were included prospectively. MMP-2 (C-737T) genotypes of both groups were determined by the restriction fragment length polymorphism method.

Results: The mean age of asthmatic patients was 48 years. The sex ratioMWW was 0.44. The frequency of patients with severe asthma is 28.6%, moderate asthma is 42.6% and mild asthma is 30.6%.

There was no difference in frequency of polymorphism of MMP-2 (C-737T) between smokers and non-smokers asthmatic patients.

Conclusion: The present study demonstrates that exposure to cigarette smoke has no influence on the polymorphism in the promoter region of MMP2. However, these results may be confirmed by further prospective studies.

PT17 Genetic typing of bronchial asthma afflicted people according to polymorphous genes for the purpose of disease progress risk factors detection
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The article presents the data concerning frequency allocation of polymorphous genes and alleles of genes belonging to family glutathione-S-transferase (GSTM and GSTT), genes of cytokines (IL-6 and TNF-A), cytotoxic receptor of T-lymphocyte gene (CTLA-4) and gene of vitamin D receptor in case of afflicted people with uncontrolled bronchial asthma clinical course.

The aim of this study: to determine the frequency allocation of polymorphous genes and alleles of the Forouzani population in different areas of Belarus. The received data concerning the frequency allocation of polymorphous genes and alleles of genes CTLA-4, TNF-A, GSTM and GSTT didn’t authentically differ from the frequency of Belarusian population.

No authentic frequency allocation differences were detected. However there were authentically proved differences in frequency allocation of polymorphous genes and alleles of genes between four polymorphous locuses of VDR-gene in case of bronchial asthma afflicted people from the one detected in the population. The VDR gene’s frequency of homozygotes FF at FokI locus (36.0%) is higher than the population’s frequency of patients with severe asthma is 28.6%, moderate asthma is 42.6% and mild asthma is 30.6%.

However, its role is not clear.

Materials and methods: We studied 180 patients with allergic BA and 180 patients with non-allergic BA. As a control, the DNA of 180 citizens’ population in different areas of Belarus. The received data concerning the frequency allocation of polymorphous genes and alleles of genes between four polymorphous locuses of VDR-gene in case of bronchial asthma afflicted people from the one detected in the population. The VDR gene’s frequency of homozygotes FF at FokI locus (36.0%) is higher than the population’s frequency of patients with severe asthma is 28.6%, moderate asthma is 42.6% and mild asthma is 30.6%.

The present study demonstrates that exposure to cigarette smoke has no influence on the polymorphism in the promoter region of MMP2. However, these results may be confirmed by further prospective studies.

PT18 The role of the epithelial barrier in allergic airway inflammation
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Aim: To identify the correlation of clinical and morphological data damage the mucous membranes of the nose and bronch in patients with asthma.

Materials and methods: We studied scrapings of the mucous membrane of the nasal cavity, lavage and bronchosbiopaty patients with allergic rhinitis (AR) and bronchial asthma (BA). A comparative analysis between a group of teenagers and adults. Scanning (SEM) and transmission electron microscopy (TEM), semi-thin sections.

Results: We have shown that the surface of the epithelial cells of the upper and lower respiratory tract in AR and BA tend to have the same changes that, along with clinical data on hyperreactivity of these departments, as determined by provocative tests, and indicates a common mechanism of damage to the epithelium. By SEM we found the greatest damage to the exposed ciliated cells (CC) and by TEM detected the most spread gaplotype is TtAaBbFf). The received data indicate the connection of VDR polymorphism with uncontrolled bronchial asthma and the utility of conducting the further research concerning the influence of vitamin D on treatment.

116s
Conclusion: The intensity of changes is directly related to the severity of the disease, its early onset, dynamics and duration of disease. This whole complex of changes suggests major modifications in the morphology of the airway in allergic response to aggression. Timely basic therapy and ASIT contribute to a better clinical effect, helps to prevent potential complications, and also helps to restore a damaged nose and bronchial mucosa.

PT19
Comonitexosion to nicotine and endotoxin in vitro induces murine airflow hyperreactivity possibly via nicotine-induced upregulation of toll-like receptors
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Introduction: Nicotine and endotoxin are important components of cigarette smoke, known to cause asthma and trigger exacerbations. The present study examined whether concomitant exposure to nicotine and endotoxin in vitro can cause airway hyperreactivity (AHR) in murine tracheal segments, and explored the involvement of Toll-like receptors (TLR) and MAPK signalling pathways in this process.

Methods: Isolated murine tracheal segments were exposed to nicotine (10 μM) and/or endotoxin (10 μg/ml) in organ culture for 4 days. Contractile responses to carbachol were recorded by myograph. In parallel, mRNA and protein expressions of the cell surface TLRs and several inflammatory mediators were semi-quantified by real-time PCR and confocal microscopy-based immunohistochemistry after exposure to only nicotine with/without specific inhibitors for MAPK pathways JNK, ERK1/2 or p38.

Results: Nicotine or endotoxin alone failed to affect contractile responses to carbachol, whereas AHR appeared after concomitant exposure. Incubation with nicotine increased expression of TLR2, 4 and 6, decreased TLR5, while TLR11 and 11 expressions remained unchanged. In parallel, MCP-1 and COX-2 expressions also increased. Inhibition of JNK, but not ERK1/2 or p38, attenuated nicotine’s effects.

Conclusion: Long-term nicotine exposure induces local inflammation and rearrangement of the airway surface TLR expression pattern via the MAPK JNK signaling dependent pathways. It is therefore tempting to suggest that the nicotine-induced up-regulation of TLR is responsible for the AHR observed after concomitant incubation with nicotine and endotoxin.

PT20
Increased cough responsiveness in guinea pigs with respiratory syncytial virus infection and its neurogenic mechanism
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Introduction: Respiratory syncytial virus (RSV) is the most common pathogen responsible for lower respiratory tract infections (LRTI) in young children. RSV infection triggers cough, whereas AHR appeared after concomitant exposure. Incubation with nicotine increased expression of TLR2, 4 and 6, decreased TLR5, while TLR11 and 11 expressions remained unchanged. In parallel, MCP-1 and COX-2 expressions also increased. Inhibition of JNK, but not ERK1/2 or p38, attenuated nicotine’s effects.

Methods: Fifty guinea pigs were randomly divided into a control group and four RSV-inoculated groups: post-infection day (PID) 6, 12, 28 and 42. Cough responsiveness, airway inflammation without pneumonia, RSV RNA content was highest at PID 6 and then gradually decreased. SP peaked at PID 28 and remained high at PID 42, SP protein staining could be seen in lung tissue. NK1 mRNA levels were also significantly increased at PID 12, 28 and 42. Cough responsiveness was positively correlated with SP and NK1 mRNA levels.

Results: Cough responsiveness of infected groups was significantly higher than control and reached a peak at PID 12. Inflammatory cells and lymphocytes increased in bronchoalveolar lavage fluid, and lung tissue pathology showed airway inflammation without pneumonia. RSV RNA content was highest at PID 6 and then gradually decreased. SP peaked at PID 28 and remained high at PID 42. SP protein staining could be seen in lung tissue. NK1 mRNA levels were also significantly increased at PID 12, 28 and 42. Cough responsiveness was positively correlated with SP and NK1 mRNA levels.

Conclusion: The increase in cough responsiveness was consistent with the clinical features of cough caused by RSV. The accompanying increase in SP and its receptor with the positive correlation between these parameters and cough responsiveness suggests that neurogenic inflammation may play a decisive role in the increase in cough responsiveness and cough induced by RSV.

PT21
Immunomodulation capacity of alpha-1 antitrypsin in regulation of CD14 molecules expression and secretion in human monocytes in vitro
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Introduction: Human monocytes CD14 expression was analysed by flow cytometry and mRNA expression were evaluated and the correlation between cough responsiveness and SP and NK1 mRNA levels determined.

Results: Cough responsiveness of infected groups was significantly higher than control and reached a peak at PID 12. Inflammatory cells and lymphocytes increased in bronchoalveolar lavage fluid, and lung tissue pathology showed airway inflammation without pneumonia. RSV RNA content was highest at PID 6 and then gradually decreased. SP peaked at PID 28 and remained high at PID 42. SP protein staining could be seen in lung tissue. NK1 mRNA levels were also significantly increased at PID 12, 28 and 42. Cough responsiveness was positively correlated with SP and NK1 mRNA levels.

Conclusion: The increase in cough responsiveness was consistent with the clinical features of cough caused by RSV. The accompanying increase in SP and its receptor with the positive correlation between these parameters and cough responsiveness suggests that neurogenic inflammation may play a decisive role in the increase in cough responsiveness and cough induced by RSV.

89. COPD: human studies

PT22
Various phenotype of COPD are closely related to regulatory T cells
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Background: Regulatory T-cells (T-reg) play an important role in physiology and pathology of immune system and take essential place in pathogenesis of various autoimmune, tumoral and allergies diseases. However, T-reg subpopulations in separate phenotypes of COPD remain insufficiently studied.

Aim and objectives: To investigate different subpopulations of T-reg in patients with various phenotypes of COPD.

Methods: Levels of natural CD4+CD25high and inducible CD4+FoxP3+ T-reg were analyzed in 60 subjects with COPD (including 13 subjects diagnosed with emphysematous phenotype, 28 patients with bronchitic phenotype, 19 subjects with mixed phenotype of COPD) and 17 healthy subjects (HS) using the flow cytometry analysis.

Conclusions: These findings provide evidence that AAT is an important regulator of CD14 expression and release in monocytes and suggest that AAT may be involved in prevention of over-activation of monocytes/macrophages in vivo, that is important in development of chronic lung diseases.

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Results: CD4+CD25+high in COPD were significantly increased compared to HS (2.8 ± 0.24%, p = 0.005; 1.56 ± 0.24%, p = 0.005, respectively). Increased level of CD4+CD25+high was shown for persons with emphysema phenotype (3.43 ± 0.46%, p = 0.001) compared to persons diagnosed with bronchial (2.3 ± 0.22%, p = 0.021) and mixed (2.38 ± 0.22%, p = 0.014) phenotypes of COPD. As for CD4+FoxP3+ T-reg no difference between different phenotypes of COPD was observed.

Conclusions: Different subpopulations of T-reg may determine various phenotypes of COPD and this study indicates that increased level of CD4+CD25+high is associated with emphysema phenotype of COPD to support this hypothesis.

P273
IL-33 has a nuclear distribution and is not increased in peripheral lung of COPD patients
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IL-33-1 (33), a member of the IL-1 cytokine family, is crucial for induction of Th2-type immune responses but is also involved in the induction of non-Th2-type inflammation as a pro-inflammatory cytokine, similar to IL-1 and IL-18. The aim of our study was to investigate by immunohistochemistry (IHC), RT-qPCR, ELISA and Western blotting (WB) the expression and the amount of IL-33 in peripheral lung, and bronchoalveolar lavage (BAL) from 15 age- and smoking history-matched smokers with normal lung function and 15 smokers with mild to moderate stable COPD not treated with ICS and/or theophylline. The IHC staining was mainly confined to the nuclei of endothelial cells and small airway epithelial cells in the IL-33+ positive cells and the level of mRNA expression was not significantly different in patients with COPD compared to controls. IL-33 was under detection limits using ELISA (BAL) and WB (peripheral lung). These data suggest that an IL-33-mediated immune response, may not be critical in COPD and its nuclear role is uncertain.

P274
Decrease of soluble adhesion molecules levels and bacterial mixt-infection in patients with COPD
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The soluble forms of intracellular adhesion molecules (sICAM) such as membrane forms are involved in modulating the cell interaction. In order to investigate adhesion disturbances the serum levels of sICAM-1 (scD54) and sICAM-3 (scD50) were analyzed in 48 patients with exacerbation of COPD and 86 healthy donors using ELISA- method. Quantitative culture of sputum or bronchoalveolar lavage fluid were performed. The median levels of scD50 and scD54 were significantly lower in COPD patients than in donors. The scD50 and scD54 values below the normal range were registered in 60% of the patients. The decrease of scICAM levels was associated with longer smoking history compared with patients having normal/elevated values, and with exacerbation of bronchitis, bacterial mixt-infections, and prolonged therapy duration. The low serum levels of the soluble adhesion molecules reflecting the impaired expression of the membrane forms can be considered as unfavorable factor.

P275
Value of serum and induced sputum surfactant protein-D in chronic obstructive pulmonary disease
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Aim: In the present study, we aimed to investigate the correlation between SP-D in serum and induced sputum and severity of COPD.

Methods: 20 healthy subjects older than 40 years of age with at least 10 pack-year smoking history (group 1), 20 stage I-II COPD patients (group 2) and 20 stage III-IV COPD patients (group 3) were enrolled to the study. All subjects performed pulmonary function tests and C-reactive protein (CRP) and blood SP-D levels measured. Induced sputum samples were obtained to determine induced sputum SP-D levels. COPD patients were followed up for exacerbation for 6 months.

Results: Serum SP-D levels of group 3 were highest and and induced sputum SP-D levels of group 2 were lowest compared among three groups. However, there were no statistically significant differences among three groups (p>0.05). SP-D levels of induced sputum decreased in patients with high number of cigarette pack-year, whereas serum SP-D levels increased in these patients (p<0.05). Induced sputum SP-D levels of COPD patients receiving inhaler corticosteroid treatment were higher than patients who were not receiving inhaler corticosteroid treatment (p<0.05). An inverse correlation between serum SP-D levels and FEV1 (L%) was found and there was a positive significant correlation between the serum SP-D levels and exacerbation frequency in 6-month follow up period in our study (p<0.05).

Conclusion: Our study demonstrates adverse effects of smoking on local SP-D levels. Low levels of local SP-D in the group of current smokers, who were not receiving inhaler corticosteroid treatment indicate the importance of airway inflammation in COPD pathogenesis.

P276
Inflammatory cytokines in induced sputum and COPD phenotype
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Chronic obstructive lung disease (COPD) does not have a uniform clinical and morphological nature. Airflow limitation is caused by inflammation and parenchymal destruction, with predominance of emphysematous phenotype and predominance of chronic bronchitis. The aim of the study was to characterize the inflammatory process in two distinct forms of COPD.

35 COPD patients were enrolled to two groups: emphysema (E, n=25) and chronic bronchitis pts (CB, n=10); the presence of emphysema in HRCT and hyperinflation in plethysmography were the distinguishing criteria. The concentration of cytokines (IL-8, IL-6, IL-10, TNF-a and IL-12) in induced sputum (IS) was measured using flow cytometry with Cytomine Bead Array method. The median concentration of proinflammatory cytokines (IL-8, IL-6, IL-10 and TNF-a) did not differ between two groups. The concentration of IL-10 and IL-12 was slightly, but not significantly, higher in the E when compared with CB group (median: 57 vs 41 pg/ml, 1553 vs 1122 pg/ml, respectively). There was a significant correlation between the concentrations of IL-8, IL-6, IL-10 and TNF-a in the CB group. When we analysed the relation of cytokine concentration with the clinical parameters, we observed a difference between the E and CB group. There was a significant correlation of IL-10, TNF-a and IL-12 concentration with the degree of emphysema (RV, TLC, Raw) and FEV1 only in the E group. A significant correlation of IL-6 concentration with pack/year, TLC and with the inflammatory cell total count was observed only in the CB group. The differences in cytokine profile and correlations indicate a possible different character of inflammation in two COPD phenotypes.

P277
Relationship between % neutrophils in induced sputum and IL-6 and TNF-a in COPD
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Introduction: The percentage of neutrophil sputum are increased in patients with Chronic Obstructive Pulmonary Disease (COPD), and is a biomarker of airway inflammation. The aim of this study is the relationship between sputum% neutrophils and levels of IL-6 and TNF-a in induced sputum in COPD with moderate-severe airflow obstruction.

Method: Sputum samples were obtained using 3% saline, according to international guidelines., from a total of 60 subjects 40 COPD patients (criteria for diagnostic and classification of disease severity based on the Global Initiative for Chronic Obstructive lung disease (GOLD) and 20 healthy men (control group) who had no story of lung disease and normal spirometry. All the patients were smokers of >20 pack/year, and were free from acute exacerbations in three months prior to the study. In each subject BMI (kg/m²), dysnea according to the modified Medical Research Council scale (MRC), oxygen saturation (SatO2), spirometry before and after 400μg inhaled salbutamol, lung volumes and carbon monoxide transfer factor coefficient (KCO) measurements were measured. TNF-a and IL-6 were measured by RIA.

Results: The sputum neutrophil% was statistic significative higher in COPD patients than group control p<0.05. We find a negative correlation between the percentage of the non-scamous cell count and% neutrophil whit the FEV1% and the% FVC/FVC<p<0.05, but not with the grade of dysnea (MRC) and SatO2. There was a weak association between sputum neutrophils and IL-6 e= 0.385, p<0.003, and TNF= 0.468 p=0.001.

Conclusion: Neutrophils in sputum in COPD patients are associated with the airflow limitation and white the levels of IL-6 and TNF-a.
P728 Expression of the phosphorylated myristoylated alanine-rich C kinase substrate (MARCKS) in COPD bronchial glands
Gaetano Caramori1, Paolo Casolar1, Elvira Garofano1, Marco Contoli2, Giulia Gnesini1, Anna Padovani1, Khan Fan Chung2, Peter J. Barnes2, Ian M. Adcock1, Alberto Papi3. 1Sezione di Malattie dell’Apparato Respiratorio, University of Ferrara, Ferrara, Italy; 2Airways Disease Section, NHRI, Imperial College London, London, United Kingdom

Myristoylated alanine-rich C kinase substrate (MARCKS) is a central regulatory molecule involved in mucin granule release by human bronchial epithe-
lial cells in vitro. Upon stimulation, activated PKC phosphorylates MARCKS (p-MARCKS), causing translocation of p-MARCKS from the plasma membrane to the cytoplasm, where it is then dephosphorylated, thus interacting with mucin granule membranes and mediating their subsequent exocytosis. The aim of our study was to investigate by immunohistochemistry (IHC) the expression of pro-	ein p-MARCKS in the bronchial rings, obtained during lung resection surgery, of smokers (current and ex) with or without COPD compared with non-smoker subjects. We examined formalin-fixed paraffin-embedded bronchial rings by IHC for identification of total p-MARCKS+ cells. The number of p-MARCKS+ve cells was determined among the mucous cells in the bronchial submucosal glands. Samples from 10 age-matched non-smokers subjects, 29 smokers with normal lung function and 29 smokers with COPD were obtained. We were unable to detect any significant differences in p-MARCKS in the bronchial mucous glands between the 3 groups of subjects. This data suggests that the p-MARCKS pathway is not critical for mucin secretion in the bronchial glands of COPD patients.

P727 The effects of morphological remodeling of the bronchi on the neocollagenesis process in patients with COPD stage 2 during exacerbation
Mykola Ostrovytsky, Oleksandr Varukhiv, Marianna Kulykhyn-Misik, Iryna Savelikhina. Internal Medicine No.8, Ivan-Frankivsk National Medical University, Ivan-Frankivsk, Ukraine

Background: Chronic obstructive pulmonary disease (COPD) is the third most common cause of death (8%) in the 25 member states of the European Union.

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death (8%) in the 25 member states of the European Union. COPD is a chronic and progressive lung disease that causes airflow obstruction. COPD is characterized by chronic respiratory symptoms and an abnormal persistent increase in sputum production.

The effects of morphological remodeling of the bronchi on the neocollagenesis process in patients with COPD stage 2 during exacerbation

Materials and methods: To study the morphological processes of bronchial re-
modelling there was conducted an electron microscopy of bronchial mucosa bioptic material that had been conducted at the bifurcation of the proximal bronchi during bronchoscopy in 9 patients with COPD stage 2 at the moment of hos-
pitalization. The content of type IV collagen was investigated in bronchoalveolar fluid of 43 patients with stage 2 COPD before and after 1, 3 and 6 months of treatment medications. Neocollagenesis was estimated by the determination of the ratio of procollagen type I and II.

Results of the study: The results of our research showed that patients with COPD on early stages (2nd stage) there were damage of bronchial mucosa, with a significant growth of connective tissue in lamina propri, which was accompanied by increased content of collagen type IV in bronchoalveolar fluid in 6.19 times compared with healthy. This is an evidence of increased activity of fibroblasts as a result of microcirculation disturbances, activation of lipid peroxidation and effects of hypoxia.

Conclusions: Due to the morphological remodeling there is great activity of neo-
collagenesis during exacerbation of COPD, evidenced by significantly increased production type IV of collagen in bronchoalveolar fluid.

P730 Differences in biomarkers of systemic inflammation in two phenotypes of COPD patients
Carmen Soto Fernández, Elena Paity Pether, Rubén Andújar Espinosa, Consuelo Alcalde Rumayor, Juan Orlando López Ojeda, Carlos Federico Álvarez Miranda, Julia Guardiola Martínez, Francisco José Ruiz López, Juan Latour Pérez, Isabel Parra Parra, Manuel Lorenzo Cruz. Pulmonology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Introduction: Classification of chronic obstructive pulmonary disease (COPD) is usually based on the severity of airflow limitation, but not the heterogeneity of this disease. The aim of this study was to establish differences in biomarkers of systemic inflammation in two phenotypes of COPD patients, through determination protein-C reactive (PCR), fibrinogen, IL-6 and TNF-a in plasma, in stable COPD.

Method: A total of 60 subjects, 40 stable COPD (diagnostic and severity based on the Global Initiative for Chronic Obstructive Lung Disease) and 20 controls. We es-
tablished two groups of patients based on the carbon monoxide gas transfer/alveolar volume (Kco) and visual detection of emphysema computed tomography (CT).

A: Phenotype emphysema (n=19), Kco>70% CE CT compatible; B: phenotype chronic bronchitis (n=21), Kco<70% and CT without emphysema. Plasmatic determination of fibrinogen, PCR, 5'neutrophils, IL-6, and TNF (RIA).

Results: The values of fibrinógeno/PCR did not show significant differences be-
tween both phenotypes of COPD (B 432±203 vs 470 mg/dl / 0.542±0.14 mg/l), (A 452±368±70.503 mg/dl / 0.842±0.935 mg/l), but were compared with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l) with controls (C 346±203±70.503 mg/dl / 0.842±0.935 mg/l). The results of our study demonstrated that CD4+/CD8+ ratio may be used as a biomarker to evaluate the pathogenesis of COPD, however TLR-2 is not convenient for this purpose.

P732 Peripheral neutrophil stiffness in severe COPD exacerbations
Ebymár Arismendi Núñez1, Tomas Luque2, Yolanda Torralba García1, Alvar Agustí1, Daniel Navajas2, Roberto Rodríguez-Roisin3. 1Pneumology/ Laboratory of Pulmonary Function, Hospital Clínic of Barcelona, 2Medical Physics, Faculty of Medicine of University of Barcelona, Barcelona, Spain

Rationale: Exacerbations of COPD (EXCOPD) are characterized by activated pulmonary neutrophils (NEUT) with potentially increased cellular stiffness. Objective: The aim of this study was to assess NEUT stiffness in patients with COPD during and after exacerbations.

Methods: 12 COPD patients (age, 70±4 yrs; 83% male; all smokers, 71±36 pack-yrs) hospitalized for EXCOPD were included. Stiffness of peripheral NEUT was assessed using the atomic force microscopy technique within the first 72 h of admission and 12 weeks after discharge (Study Group [SG]). If patients suffered a new episode within this period of follow-up, measurements were repeated at this time in mean (mean, 7±4 weeks) (Re-exacerbation Group [RGI]). The COPD As-
essment Test (CAT), the ADQ Index and dyspnoea (MMRC) were also assessed.

Results: There were no differences on admission between the two subsets of patients. Increased NEUT stiffness in SG patients (n, 6) decreased from admission (890±293 Pa) to discharge (616±229 Pa) (p<0.05) compared to that measured in the RG subset (n, 6) (from 999±424 to 842±343 Pa). The ADI Index was associated with NEUT stiffness on admission in the two subsets of patients (ρ=0.60, p<0.05).

Conclusions: Changes in peripheral NEUT stiffness during COPD exacerba-
tions and convalescence indicate that the activation of NEUT underlies enhanced pulmonary inflammation. Supported by SEPAR-2010 and CIBERES

P733 Increase of extracellular IL-17A and anti-microbial peptides in the peripheral airways of smokers
Permina Glader1, Barbro Dahlén2, Bo Billing3, Lena Palmberg3, Ann-Sofie Lantz2, Kjell Larsson3, Anders Lindén1. 1Lung Immunology Group, Department of Internal Medicine/Respiratory Medicine & Allergology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 2Division of Respiratory Medicine & Allergy at the Department of Medicine, Karolinska University Hospital, Stockholm, Sweden; 3Unit of Lung and Allergy Research, National Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

Among several known cytokine-signalling pathways influencing innate effector

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cells, T helper (Th) 17 cytokines have emerged as particularly interesting for the understanding of chronic inflammatory conditions. Cigarette smokers suffer from frequent infections, are often colonised with bacteria in their lower airways and display signs of chronic inflammation including increased tissue expression of the Th17 cytokine IL-17A. We evaluated whether long-term current cigarette smokers display increased extracellular concentrations of Th17 cytokines and how this relates to anti-microbial peptides in the peripheral airways.

Concentrations of IL-17A, IL-17F and -22 plus the downstream effector molecules IL-22, IL-28 and IL-10 were measured in induced sputum from smokers and from non-smokers with and without COPD (n=17-20/group). All study subjects were free from airway infections during the last 4 weeks prior to the study.

The extracellular IL-17A concentrations (median [range]) were higher in smokers without COPD (1.2 [0.3-3.5], pg/ml) than in non-smokers (0.4 [0.1-4.4], pg/ml; p<0.05). Smokers with COPD displayed intermediate concentrations of IL-17A (0.7 [0.1-7.1], pg/ml) compared to non-smokers (22 [4-384], pg/ml). HBBD2 was higher in smokers without COPD (70 [6-500], pg/ml; p<0.05), but not in smokers with COPD (24 [4-364], pg/ml). Interleukin-17F, IL-22 and LL37 were undetectable in most of the samples.

In conclusion, long-term cigarette smokers without COPD display increased extracellular concentrations of IL-17A, and this may be linked to increased concentrations of the anti-microbial peptide HBBD2.

P734 Comparison of arterial cellular and mediator profiles between tobacco smoke-induced COPD and biomass fuel exposure-induced COPD in an Indian population

Bill Brashier1, Nitin Vanjare1, Jyoti Londhe 1, Sapna Madas 1, Sanjay Juvekar 2, Sundeep Salvi1, Peter Barnes 3.

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Introduction and background: Chronic obstructive pulmonary disease (COPD) is characterized by specific pattern of inflammation involving polymorphonuclear neutrophils (PMNs), macrophages and other cells. PMNs are the major reactive oxygen species (ROS) producing cells. Our previous data showed that ROS production is decreased in stable COPD (SCOPD). It is still not known about ROS production in acute exacerbation of COPD (AECOPD).

Aim: To investigate ROS production in PMN during AECOPD.

Methods: 10 patients with SCOPD, 5 with AECOPD and 10 non-smoking healthy individuals (HI) were studied. PMNs were isolated from peripheral blood using a high-density gradient. ROS production was induced using phorbol-myristate-acetate (PMA, 0.1-3.0 nM) and S. aureus bacteria (1-167 bacteria/neutrophil). ROS production was measured using flow cytometry by mean of fluorescence intensity in PMN population.

Results: The production of spontaneous ROS in PMN was 29.7±4.1% higher in AECOPD group than in SCOPD (p<0.05). PMA stimulated ROS production in all groups. The most significant increase of ROS production was observed between 0.3 and 1 nM PMA (AECOPD 172.5-fold, SCOPD 90.1-fold, HI 46.2-fold (p<0.05)). The higher ROS production in PMN after stimulation with different S. aureus concentrations was found in AECOPD group compared with SCOPD and HI (p<0.05).

Conclusion: Our data shows that ROS production is increased in AECOPD. Chemical (PMA) and biological (S. aureus bacteria) factors activates more intensive ROS generation.

P735 Vascular dysfunction and systemic inflammation in patients with COPD

Felipe Villar-Alvarez, Germán Ponce-Barba, Julio Gómez-Seco, María Jesús Rodríguez-Nieto, María Vascular dysfunction and arterial stiffness were unpredictive.

In the alveolar space the presence of an extracellular, biologically active ROS producing cells. Our previous data showed that ROS production is decreased in stable COPD (SCOPD). It is still not known about ROS production in acute exacerbation of COPD (AECOPD).

Existence of repair mechanisms resulting in bronchial and alveolar protein degradation induced by smoke exposure are largely unknown. In the alveolar space the presence of an extracellular, biologically active ROS is predicted to increase ROS production in acute exacerbation of COPD. However, our previous data showed that ROS production is decreased in stable COPD (SCOPD). It is still not known about ROS production in acute exacerbation of COPD (AECOPD).

Methods: Sixteen adult subjects underwent bronchoscopy for AECOPD (n=17-20). All study subjects were free from airway infections during the last 4 weeks prior to the study.

The extracellular IL-17A concentrations (median [range]) were higher in smokers without COPD (1.2 [0.3-3.5], pg/ml) than in non-smokers (0.4 [0.1-4.4], pg/ml; p<0.05). Smokers with COPD displayed intermediate concentrations of IL-17A (0.7 [0.1-7.1], pg/ml) compared to non-smokers (22 [4-384], pg/ml). HBBD2 was higher in smokers without COPD (70 [6-500], pg/ml; p<0.05), but not in smokers with COPD (24 [4-364], pg/ml). Interleukin-17F, IL-22 and LL37 were undetectable in most of the samples.

In conclusion, long-term cigarette smokers without COPD display increased extracellular concentrations of IL-17A, and this may be linked to increased concentrations of the anti-microbial peptide HBBD2.

Conclusion:

P736 Influence of AECOPD to ROS production in neutrophils

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Introduction and background: Chronic obstructive pulmonary disease (COPD) is characterized by specific pattern of inflammation involving polymorphonuclear neutrophils (PMNs), macrophages and other cells. PMNs are the major reactive oxygen species (ROS) producing cells. Our previous data showed that ROS production is decreased in stable COPD (SCOPD). It is still not known about ROS production in acute exacerbation of COPD (AECOPD).

Aim: To investigate ROS production in PMN during AECOPD.

Methods: 10 patients with SCOPD, 5 with AECOPD and 10 non-smoking healthy individuals (HI) were studied. PMNs were isolated from peripheral blood using a high-density gradient. ROS production was induced using phorbol-myristate-acetate (PMA, 0.1-3.0 nM) and S. aureus bacteria (1-167 bacteria/neutrophil). ROS production was measured using flow cytometry by mean of fluorescence intensity in PMN population.

Results: The production of spontaneous ROS in PMN was 29.7±4.1% higher in AECOPD group than in SCOPD (p<0.05). PMA stimulated ROS production in all groups. The most significant increase of ROS production was observed between 0.3 and 1 nM PMA (AECOPD 172.5-fold, SCOPD 90.1-fold, HI 46.2-fold (p<0.05)). The higher ROS production in PMN after stimulation with different S. aureus concentrations was found in AECOPD group compared with SCOPD and HI (p<0.05).

Conclusion: Our data shows that ROS production is increased in AECOPD. Chemical (PMA) and biological (S. aureus bacteria) factors activates more intensive ROS generation.

P737 Acute smoke exposure decreases bronchial extracellular proteasome concentration

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Existence of repair mechanisms resulting in bronchial and alveolar protein degradation induced by smoke exposure are largely unknown. In the alveolar space the presence of an extracellular, biologically active ROS is predicted to increase ROS production in acute exacerbation of COPD. However, our previous data showed that ROS production is decreased in stable COPD (SCOPD). It is still not known about ROS production in acute exacerbation of COPD (AECOPD).

Methods: Sixteen adult subjects underwent bronchoscopy for AECOPD (n=17-20). All study subjects were free from airway infections during the last 4 weeks prior to the study.

The extracellular IL-17A concentrations (median [range]) were higher in smokers without COPD (1.2 [0.3-3.5], pg/ml) than in non-smokers (0.4 [0.1-4.4], pg/ml; p<0.05). Smokers with COPD displayed intermediate concentrations of IL-17A (0.7 [0.1-7.1], pg/ml) compared to non-smokers (22 [4-384], pg/ml). HBBD2 was higher in smokers without COPD (70 [6-500], pg/ml; p<0.05), but not in smokers with COPD (24 [4-364], pg/ml). Interleukin-17F, IL-22 and LL37 were undetectable in most of the samples.

In conclusion, long-term cigarette smokers without COPD display increased extracellular concentrations of IL-17A, and this may be linked to increased concentrations of the anti-microbial peptide HBBD2.

Conclusion:

References:


**P738**

**Neutrophil phagocytic activity in AECOPD**

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**Background:** Neutrophils are the major inflammatory cells in pathogenesis of chronic obstructive pulmonary disease (COPD). It is known that phagocytic activity of these cells is decreased during stable COPD (SCOPD). Otherwise, it is unknown how neutrophils act in acute exacerbation of COPD (AECOPD).

**Aim:** To investigate neutrophils phagocytic activity in AECOPD.

**Methods:** Patients with SCOPD, 7 with AECOPD and 10 healthy individuals (HI) were studied. Neutrophils were isolated from peripheral blood by high-density ficoll. Phagocytosis was investigated using different concentrations of FITC labeled S. aureus bacteria (1-167 bacteria/neutrophil (b/n)). Phagocytic activity was analyzed using flow cytometry assessing the cellular immunofluorescence intensity of these population.

**Results:** Neutrophil phagocytic activity was decreased in patients with AECOPD in comparison with SCOPD and HI. The highest phagocytosis was obtained using 167 b/n concentration in AECOPD and SCOPD groups (6.52±2.5-fold and 8.84±1.8-fold), but phagocytic activity was lower compared with HI (13.5±2.2-fold) (p<0.05).

**Conclusion:** Our results shows that neutrophils phagocytosis is decreased during AECOPD.

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**P739**

**LSC 2011 Abstract: Suppression of antitumor immunity as a potential link between inflammation and cancer in COPD**

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Asthma and COPD are chronic obstructive diseases with a certain degree of physiologic and pathologic similarities. Our previous work demonstrated that these diseases could be phenotypes of the same process. This hypothesis has never been universally accepted due to the evident differences between the two diseases. However COPD has two distinct pathologic phenotypes, Panlobular Emphysema (PLE) where airflow obstruction is secondary to loss of elasticity and Centrilobular Emphysema (CLE) where airflow obstruction is secondary to bronchial remodeling with increased muscle and smaller diameter. We hypothesise that CLE could have features of Asthma different from PLE, especially as far as mast cells (MC) inflammation and their relation to airway reactivity.

Therefore, we quantified tryptase stained MC in all patients in submucosa, smooth muscle and adventitia of small airways in 27 lungs with CLE, 24 with PLE, and 5 healthy individuals (NS). The proportion of MC in smooth muscle of small airways were significantly higher in CLE (206±41 cells/mm²) than in PLE (104±21 cells/mm²; p=0.011; SME 107±54 cells/mm²; p=0.05) and NS (105±27 cells/mm²; p=0.05). Moreover, the degree of MC infiltration in the smooth muscle was related with the degree of hyperresponsiveness, as it has been shown in Asthma (PC20 3-8mg/ml: 206±41 cells/mm²; p=0.011; SME 107±54 cells/mm²; p=0.05) and NS (105±27 cells/mm²; p=0.05).

**Conclusion:** These results give support to the hypothesis of the potential link between inflammation and cancer in COPD.

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**P740**

**LSC 2011 Abstract: BAFF in the interaction between T regulatory and B cells in COPD**

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The fibrogenic cytokine transforming growth factor-1 (TGF-β1) is an important mediator in airway remodelling. TGF-β1 overexpression in mice induces airway smooth muscle (ASM) hyperplasia, one of the characteristics of airway remodeling in asthma. The mechanisms underlying this overexpression of ASM cell proliferation showed that TGF-β1 alone has very weak mitogenic properties, combined effects with other factors such as Gq or Gi protein coupled receptor agonists may be involved. Here, we hypothesized that the mitogenic effects of TGF-β1 on ASM are indirect and require prolonged exposure to allow deposition of extracellular matrix (ECM) proteins. To address this hypothesis, we investigated the effects of acute and prolonged treatment with TGF-β1 (2 ng/ml), alone and in combination with PDGF and non-smokers (NS) (20, 6-95; p=0,001).

Methods: BAFF expression in B-lymphocytes and Tregs from bronchoalveolar lavage (BAL) and blood was quantified by Flow Cytometry in 38 patients with COPD (mean±SD:EV1=58±145%;p<0.05); 17 smokers with normal lung function (SC) (EV1=104±159%;p<0.05) and 20 non-smokers (NS) (EV1=101±206%;p<0.05). Conversely, BAFF was overexpressed in B lymphocytes from COPD patients (50, 23-121) when compared to SC (12, 0-28; p=0.003) and NS (20, 26-95; p<0.001).

Conclusions: In COPD there is a blunted expression of BAFF in Tregs that leads, partly due to cigarette smoke, to its excessive production in NS. MC lymphocytes, showing an imbalance of its functioning that is a common feature of several autoimmune diseases.

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**90. Airway smooth muscle cells and fibroblasts: cell biology**

**P741**

**TGF-β1-induced extracellular matrix production enhances airway smooth muscle cell proliferation**

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The fibrogenic cytokine transforming growth factor-1 (TGF-β1) is an important mediator in airway remodelling. TGF-β1 overexpression in mice induces airway smooth muscle (ASM) hyperplasia, one of the characteristics of airway remodeling in asthma. The mechanisms underlying this overexpression of ASM cell proliferation showed that TGF-β1 alone has very weak mitogenic properties, combined effects with other factors such as Gq or Gi protein coupled receptor agonists may be involved. Here, we hypothesized that the mitogenic effects of TGF-β1 on ASM are indirect and require prolonged exposure to allow deposition of extracellular matrix (ECM) proteins. To address this hypothesis, we investigated the effects of acute and prolonged treatment with TGF-β1 (2 ng/ml), alone and in combination with PDGF and non-smokers (NS) (20, 6-95; p=0,001).
P743

Omalizumab inhibits IgE-induced extracellular matrix deposition by asthmatic airway smooth muscle cells
Michael Roth, Michael Tamm, Peter Borger.

P744

Neo-vascularisation in asthma: Altered angiogenic potential of ASM cells from asthmatic patients
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P745

Carrier-mediated transport of tiotropium in bronchial smooth muscle cells
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P746

Role of endosomal and cystolic pattern recognition receptors in dsRNA-induced cytokine expression in human airway smooth muscle cells
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P747

The YKL-40-positive bronchial smooth muscle cell proliferation and migration is PAR-2 dependent
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YKL-40 was kindly provided by MedImmune. Human BSM cells were cultured from controls (n=7) and asthmatics (n=6). BSM cell proliferation was assessed using BrdU incorporation. Cell migration was evaluated using inserts. Transduction mechanisms were assessed using several inhibitors of signal transduction pathways (Pertussis toxin, Calphostin, PD98059, SB203580, LY294002). The involvement of protease activated receptor-2 (PAR-2) was evaluated using an anti-PAR-2 blocking antibody.

Results: YKL-40 significantly increased by more than two fold BSM cell BrdU incorporation in 24h incubation and cell number within 48h. Following 24h incubation, YKL-40 significantly increased BSM cell migration. These effects were inhibited by blocking PAR-2 antibody in both asthmatic and control BSM cells. Transduction mechanisms of cell proliferation and migration involved Gi protein, protein kinase C, MAPK/ERK pathways.
Conclusion: These results confirm that the chitinase YKL-40-induced BSM cell hyperplasia was PAR-2-dependant.

P748
Airway smooth muscle cells from patients with COPD exhibit a higher degree of cellular proliferation and steroid insensitivity than that from healthy patients
Mark Perry, Josie Baker, Kian Fan Chung, National Heart & Lung Institute, Imperial College London, London, United Kingdom

Rationale: Chronic obstructive pulmonary disease (COPD) refers to chronic bronchitis and emphysema, a pair of two commonly co-existing diseases of the lungs in which the airways become narrowed. The potential contribution of airway smooth muscle to airflow obstruction, airway inflammation and airway remodeling in COPD isn’t fully understood. Indeed, although it is known that the cytochrome TGF-β induces the expression of such cytokines as IL-6 and IL-8, little is known regarding its role upon ASM proliferation and steroid insensitivity in COPD. Ergo, we have examined the role of both the growth factor FCS and TGF-β, upon ASM proliferation and steroid response following treatment with dexamethasone.

Methods: Human ASM cells were pre-treated with dexamethasone for 2 h before being stimulated with FCS ± TGF-β for 8 days. For the determination of chemokine release, supernatants were removed and IL-6 levels determined by DuoSet ELISA (R&D Systems). The degree of cell proliferation was assessed by Cell Proliferation ELISA, BrdU kit (Roche Applied Science) according to the manufacturer’s instructions.

Results: Exposure to FCS and TGF-β induced a higher increase in cellular proliferation and IL-6 release in ASM from patients with COPD compared to healthy individuals. Furthermore, the inhibitory effect of dexamethasone in this system was almost completely abated in the ASM cells from the COPD patients.

P749
miR-221 and miR-222 target p21 and p27 in airway smooth muscle to elicit hyper proliferation in severe asthmatics
Mark Perry, Josie Baker, Kian Fan Chung, National Heart & Lung Institute, Imperial College London, London, United Kingdom

Rationale: Since microRNAs (miRNAs) were first discovered to be produced in humans 10 years ago, they have emerged as important mediators in cellular physiology and pathology. Asthma is characterised by chronic airflow obstruction, chronic airway inflammation and remodeling and the airway smooth muscle (ASM) cells cultured from the biopsies of patients with asthma are of a hyperproliferative phenotype. Inasmuch as miRNAs have been found to be amongst the highest differences in the expression of the chemokine IL-6. This ASM proliferation has been shown to be increased in response to growth factors such as FCS, and inflammatory mediators such as TGF-β. Ergo, we have examined the role of the miRNAs, miR-221 and miR-222, in both FCS and TGF-β-induced ASM proliferation and IL-6 release.

Methods: Human ASM cells were stimulated with FCS ± TGF-β for 8 days. For the determination of chemokine release, supernatants were removed and IL-6 levels determined by DuoSet ELISA (R&D Systems). The degree of cell proliferation was assessed by Cell Proliferation ELISA, BrdU kit (Roche Applied Science) according to the manufacturer’s instructions. miRNA and mRNA expression was examined by TaqMan RT-PCR. The function of miR-221 and miR-222 were assessed through transfection with miRNA mimics and inhibitors.

Results: Exposure to FCS and TGF-β induced an increase in cellular proliferation, IL-6 release and p21 mRNA expression in ASM cells cultured from the biopsies of COPD patients. This increase was greater in patients with severe asthma than those with non-severe asthma. FCS and TGF-β-induced proliferation and IL-6 release were inhibited following transfection with miRNA-222 inhibitors and potentiated in the presence of miRNA-222 mimics, by the targeting of p21 and p27.

P750
Sphingosine-1-phosphate receptor expression and signalling in human airway smooth muscle cells
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Sphingosine-1-phosphate (SIP), a bioactive lipid and ligand for five G protein coupled receptors (S1P1-S1P5), is a key regulator of cell trafficking, cell differentiation and immune responses. Recently, increased concentrations of S1P have been detected in airways of asthmatic subjects and S1P has been shown to be a potent constrictor of human airway smooth muscle (HASM) cells. The aim of this study was to investigate the expression and signalling pathways of S1P receptors in HASM cells. HASM cells have been grown from bronchial biopsies of healthy individuals. Real-time PCR has been used to determine gene expression. Intracellular signalling in response to SIP was measured using MAP kinase phosphorylation, intracellular calcium AMP assay. Three of the five known receptors are expressed in HASM cells at mRNA level: S1P1, S1P2, and S1P3. SIP potently activated intracellular calcium flux in a concentration-dependent manner, with EC50=4–10^(-9)M. Using a range of selective agonists and antagonists, S1P1 and S1P3 were found to couple to Gi and inhibit forskolin induced cAMP generation, whereas S1P2 and S1P1 signalled through intracellular calcium mobilisation. SIP also induced phosphorylation of extracellular signal-regulated kinase (Erk) and increased expression of several genes, including interleukin-6. This study demonstrates that S1P receptors may signal effectively through multiple intracellular pathways in response to SIP and activate HASM cells.

P751
Heme-oxygenase (HO-1) inhibitors induce CXCL10 secretion by airway smooth muscle cells
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Background and purpose: CXCL10 induces mast cell migration towards airway smooth muscle bundles in asthma. In blood mononuclear cells, induction of heme oxygenase (HO-1) inhibited pro-inflammatory cytokine secretion. Dimethyl-fumarate (DMF), which is clinically used as an anti-inflammatory medication, induced HO-1 and thereby inhibited proliferation in airway smooth muscle cells (ASMC).

Experimental approach: Here we assessed the anti-inflammatory effect of DMF on TNF-α induced CXCL10 secretion in human primary ASMC and the involvement of HO-1 and mitogen activated protein kinases (MAPK). ASMC were pre-incubated with DMF and/or glutathione ethylester (GSH-OEt), SB203580, or the HO-1 inducer hemin, or cobalt-protoporphyrin (CoPp) 1 hour before stimulation with TNF-α (10 ng/ml).

Key results: TNF-α induced the secretion of CXCL10, which was inhibited by DMF as well as by the HO-1 inducer hemin, or CoPp. Interestingly, DMF amplified the TNF-α induced phosphorylation of p38 MAPK and thereby induced the expression of HO-1. Inhibition of p38 MAPK by SB203580, reduce DMF-induced HO-1. Importantly, GSH-OEt supplementation: (i) abrogated the inhibitory effect of DMF on TNF-α induced CXCL10 secretion, (ii) counteracted DMF-induced HO-1 expression, and (iii) p38 MAPK activation.

Conclusion and implications: Our data indicate that DMF inhibits TNF-α induced CXCL10 by altering intracellular GSH, leading to activation of p38 MAPK and subsequent synthesis of HO-1 in ASMC. Thus, DMF might help to reduce airway inflammation in asthma.

P752
Corticosteroid insensitivity and enhanced mitogen-activated protein kinase activity in airway smooth muscle cells of severe asthma
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Background: Patients with severe asthma are less sensitive to oral or inhaled corticosteroids. Relative corticosteroid insensitivity has been shown in peripheral blood mononuclear cells and alveolar macrophages in these patients.

Aims and objectives: Determine the response of corticosteroids in airway smooth muscle cells (ASMCs) of severe asthma, in terms of suppression of cytokine-induced chemokine release and mRNA expression, and investigate the underlying mechanisms.

Methods: ASMCs of non-asthmatics (NA); 12 patients with non-severe (NSA); 10 or severe asthma (SA); 10 were pretreated with dexamethasone (Dex; 10^-6,10^-5 M) followed by stimulation with TNF-α at 10 ng/ml. IL-8 and eotaxin release determined by ELISA; mRNA quantified by RT-PCR. The role of corticosteroids was measured by ChIP assay; p38, JNK, and ERK expression measured by Western blot.

Results: Baseline and TNF-α induced eotaxin release and mRNA were higher in NSA, but not SA, compared to NA, while no differences were observed for IL-8. p65 recruitment to gene promoters did not differ. Dex (10^-5 M) suppressed induced eotaxin release by 36.7% vs 16.7% (p<0.05) in NSA and SA, respectively. Dex (10^-4 M) suppressed induced IL-8 release by 49.8% vs 25.7% (p<0.01) in NA and SA, respectively. Induced IL-8 and eotaxin mRNA was significantly inhibited by Dex (10^-5 M) in NA and NSA (p<0.05) but not in SA. Induced phosphorylated p38 and JNK were significantly higher in SA compared to NA, respectively (p<0.05).

Conclusions: Corticosteroid insensitivity exists in ASMCs of severe asthma, which may be associated with enhanced p38 and JNK activity.

P753
MAP kinases mediate FGF-induced expression and release of VEGF in human airway smooth muscle cells: The role of azithromycin
Anna Willems-Widyastuti1, Bart Vanaudenaerde1, Robin Vos1, Stephanie De Vleeschauwer 1, Annemie Vaneylen1, Willem de Boer 2, Haris S. Sharma3, Geert Verleden1.

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Background: Fibroblast growth factors, FGF-1, FGF-2 and vascular endothelial growth factor (VEGF) are elevated in chronic inflamed airways. Airway smooth muscle (ASM) cells are known to synthesize VEGF. We investigated the contribution of FGF-1/2 on the VEGF production in ASM cells, the involvement

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of mitogen-activated protein kinase (MAPK) and the modulatory effects of azithromycin and dexamethasone.

Methods: Human ASM cells were treated with 10ng/ml of FGF-1 or FGF-2. Specific blockers for ERK1/2 MAPK (U0126), p38 MAPK (SB203580), JNK (curcumin), dexamethasone or azithromycin were added 30 minutes prior to stimulation. Expression of VEGF (VEGF-A, VEGF-121 and VEGF-165) was assessed by quantitative PCR. VEGF release by ELISA and MAPK phosphorylation by Western Blotting.

Results: FGF-1/2 upregulated mRNA expression of VEGF (VEGF-A, VEGF-121 and VEGF-165) and its release by 1.8 fold (FGF-1) and 6.1 fold (FGF-2). Transient increase in VEGF-121 and p38 MAPK phosphorylation and subsequent release of VEGF from FGF-1/2 treated human ASM cells was inhibited by respective blockers. Furthermore, both dexamethasone and azithromycin reduced the VEGF secretion mediated by the p38 MAPK pathway.

Conclusion: Our Results demonstrate that FGF-1 and FGF-2 upregulate VEGF production via ERK1/2 MAPK and p38 MAPK pathways. The anti-angiogenic effect of dexamethasone and azithromycin may potentially contribute to VEGF-mediated vascular remodelling in chronic airway diseases.

P754 Effects of formoterol on TGF-β1 induced factors of extracellular matrix composition
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Introduction: COPD is characterised by chronic airway inflammation resulting in extensive airway remodelling. The origin of the remodelling pathology in COPD is unknown and may result from increased EMT (epithelial-mesenchymal transition). EMT of airway smooth muscle cells (ASMC) is mediated by hypoxia, cytokines and several growth factors, such as transforming growth factor-beta (TGF-β1). Formoterol is a long acting beta2 agonist which can exert anti-inflammatory effects by the regulation of intracellular cAMP levels. The aim of our study was to determine if formoterol can modulate downstream mediators of EMT by cAMP induction.

Methods: Human bronchial smooth muscle cell culture was performed using standard protocols. Cells were stimulated with Formoterol (10−10 to 5 μM), Dideoxyadenosin (DDA, 100μM), and/or Forskolin (10μM). Forskolin was used as a positive control. cAMP measurement was performed by ELISA (at 1, 3 and 6 hours) and Western Blotting. Gene expression was evaluated by real time PCR (18S mRNA served as reference gene). All experiments were performed as triplicates.

Results: Formoterol significantly increased intracellular cAMP after 1, 3 and 6 hours compared to untreated cells, whereas the maximum effect was observed after 1 hour. The cAMP increase was effectively blocked by the addition of DDA at any time point. After 24 hours, Formoterol significantly reduced TGF-β1 stimulated Col1 and CTGF mRNA transcription. The addition of DDA reversed this effect for Col1 but not for CTGF.

Conclusion: Treatment with formoterol resulted in a decrease of TGF-β1 induced mediators of extracellular matrix composition. These new findings suggest a potential role for formoterol in EMT.

P755 LSC 2011 Abstract: Potential anti-inflammatory role of the cAMP effectors Epac and PKA on TGF-β1 induced factors of extracellular matrix remodelling
Anouk Oldenburger, Sara Roscioni, Esther Jansen, Mark Menzen, Eleni Papakonstantinou1, Ioannis Klagas 1, Nicola Miglino 2, Patricia Ramos-Ramírez 3, Norma A. Bobadilla 2, Maria G. Campos 3, Fernando Gonzalez-Aguilar 3, Norma A. Bobadilla 2, Maria G. Campos 3, Ricardo Lascuarn, Eva Ramirez, Maria P. Plaza, Mayra D. Alvarez-Santos, 1, Patricia Ramos-Ramírez 3, Blanca Baran-Pereiras 1. 1Airway Hyperresponsiveness Department, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico; 2Molecular Physiology Unit, Universidad Nacional Autónoma de México, Mexico, Mexico; 3Biochemistry Department, Universidad Nacional Autónoma de México, Mexico, Mexico; 4Research in Autoimmunity, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico; 5Pharmacology Department, Instituto Mexicano del Seguro Social, Mexico, Mexico

Caveolin-1 (Cav-1) is an important signalling scaffold protein involved in smooth muscle contraction; however, the role of Cav-1 in airway responsiveness has not been elucidated so far. Our aim was to determine the relation of Cav-1 expression with airway hyperresponsiveness (AHR) in a guinea pig asthma model. To evaluate this relation, three inhaled antihistamine challenges were applied every 10 days to antigen (ovalbumin); OVA) sensitized guinea pigs (n=9). Antigen-induced airway obstruction, AHR, was measured by cone-shaped, whole body plethysmography and the expression Cav-1 in lung tissue, airway smooth muscle cells (ASM), was evaluated at the third OVA challenge. The control group received saline solution instead of OVA (n=6). From the first challenge on, OVA induced a transient airway obstruction and the development of AHR at the third antihistamine challenge, Cav-1 mRNA levels in lung (assessed by RT-PCR) significantly decreased in our asthma model compared with the control group (P<0.01). Nevertheless, in the ASM from allergic asthma guinea pigs, the expression of Cav-1 mRNA, determined by PCR “in situ”, was increased. This increment was confirmed by flow cytometry in ASM and by immunohistochemistry in lung tissue. Airway obstruction and AHR were correlated with the extent of Cav-1 expression, which is mediated by Epac1 (r=0.69 and 0.52, respectively). Our data suggest that Cav-1 expression in ASM has a crucial role in airway obstruction magnitude and in the process of AHR in this asthma model.

P756 Relaxant effect of coccus sartus (saffron) on guinea pig tracheal chains and its possible mechanism(s)
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The relaxant effects of 4 cumulative concentrations of aqueous-extract of Coccus sartus and safranal were examined by their relaxant effects on precontracted tracheal chains of guinea pig by 10 μM methacholine (group 1) and 60 mM KCl in the presence of different conditions including the presence of 1 mM propranolol and 1 μM chlorpheniramine and 1 μM atropine (group 3, n=6). In groups 1 and 2 all concentrations of theophylline, extract and safranal showed significant relaxant effects compared to that of saline (p<0.05 to p<0.001). However, in group 3 the extracts of Coccus sartus showed a weak relaxant effect (p<0.05 only for highest concentration). The effects of last concentrations of safranal in group 1, and its all concentrations in group 2 were significantly lower than those of theophylline (p<0.05 to p<0.001). In addition to the effects of two last concentration of safranal in both groups 1 and 2 were significantly lower than that of Coccus sartus extract. These results showed a potent relaxant effect of Coccus sartus on tracheal chains of guinea pigs. The results also indicated the safranal is at least, in part, responsible for the relaxant effect of Coccus sartus.
Conclusion: Our results indicate that cigarette smoke induces HA catabolism which may lead to increased inflammation in the lung through low molecular weight HA molecules.

P759
Roфhumilast N-oxide, a PDE4 inhibitor, curbs bleomycin-induced lung fibroblast activation in vitro
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Objective: Activated lung fibroblasts may foster small airway thickening in COPD. Roфhumilast, an oral, selective PDE4 inhibitor approved in EU for severe COPD, mitigates bleomycin (BLM)-induced lung fibrosis in vivo. This study addressed whether roфhumilast N-oxide (RNO), the active metabolite of roфhumilast, modulates effects of BLM on human lung fibroblasts (HLF) in vitro. RNO was used at 2nM corresponding to therapeutic plasma levels.

Methods: HLF pre-incubated with RNO (2nM) were exposed to BLM for 24 or 48h. Reactive oxygen species (ROS) were measured by 2′,7′-dichlorodihydrofluorescein (DCF) accumulation from dichlorodihydrofluorescein diacetate. Total glutathione (GSH) was measured with the GSH reductase DTNB protocol. Proliferation and collagen synthesis was assessed as [3H] thymidine and [3H] proline incorporation (+p<0.05 vs control; *p<0.05 vs BLM).

Results: BLM (24h) at 50 and 100μg ml⁻¹ enhanced DCF accumulation by 1.9±0.4± control. RNO (2nM) reduced this increment by 50%±8%±, respectively. In parallel, total GSH was reduced by BLM (100 μg ml⁻¹) yet rescued by RNO (2nM) (nmol mg protein⁻¹: Control 72±1.1, BLM 26.6±1.3*, RNO+BLM 25±1.7). BLM+2nM RNO 30±1.7, BLM (50 μg ml⁻¹) increased [3H] thymidine incorporation in HLF by 1.4± control. RNO (2nM) rescued this effect. Finally, RNO (2nM) reduced [3H] proline incorporation that was increased to 179±135% of control (100 μg ml⁻¹) with 83±136% of control. RNO (2nM) did not affect basal GSH, total GSH [3H] thymidine or [3H] proline incorporation.

Conclusions: BLM augmented ROS formation, reduced total GSH and increased proliferation and collagen synthesis of HLF in vitro. RNO (2nM) prevented these effects.

P760
Fibroblast cell behaviour growing into a stiffened three dimensional collagen matrix
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Introduction: Idiopathic Pulmonary Fibrosis is a process that involves abnormal cell behaviour and increased tissue stiffness. The aim of this study was to elaborate a stiffened three-dimensional (3D) collagen I matrix to study cultured human cell inside.

Methods: 3D matrices were elaborated with native collagen I and it was non-enzymatically glycated with ribose at different conditions. Matrix stiffness was measured with Atomic Force Microscope and collagen deposition was evaluated by confocal reflexion microscopy. Primary fibroblasts were obtained from normal human lungs. Cellular viability in 3D matrices was evaluated by AlamarBlue fluorescence assay and LIVE/DEAD kit at different time points.

Results: It was observed that fluorescence AlamarBlue assay requires more time incubation to detect viability in 3D collagen matrices than in 2D cultures. An increased stiffness of 3D matrices was achieved with high concentration of collagen and ribose glycation from the second week. Stiff-variability and morphological changes in collagen I fibers was dependent on the media used for the matrix elaboration and the glycation condition. Cell death was detected in higher ribose concentrations. Fibroblasts showed a better-defined morphology and viability in matrices elaborated with lower ribose concentrations and DMEM media.

Conclusion: The development of this 3D collagen I matrix allows the fibroblast growth inside a modified microenvironment. Cell viability depends on different variables and it dramatically decreases with higher concentrations of ribose. This innovated model could help in the study of cell behaviour and phenotype at different conditions. Supported by: SEPAR, SOCAP, FUCAP, PS0801757

P761
Tiotropium reduced carbachol-induced expressions of IL-6 and IL-8 by primary human lung fibroblasts of asthma and non-asthma subjects
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Asthma is a reversible, obstructive airway disease of unknown etiology. Although the molecular pathology of asthma is still obscure, muscarinic receptor antagonists are currently in use to treat the disease. Human lung fibroblasts express muscarinic receptors, which may regulate and fine-tune the expression of cytokine genes. In the present study we analyzed the effect of the muscarinic receptor agonist, carbachol, on the release of IL-8 and IL-6 by primary human lung fibroblasts obtained from asthmatic and non-asthmatic subjects. Fibroblasts were grown in RPMI-1640 (±10% FCS, ±1% vitamins) in the presence of increasing carbachol concentrations (10-8M to 10-6M). Carbachol dose-dependently and significantly inhibited IL-6 release in IL-1β-stimulated fibroblasts of non-asthmatics, but not in fibroblasts of asthmatic patients. Furthermore, Carbachol dose-dependently increased the IL-1β-induced IL-8 release, however, with no difference comparing fibroblasts obtained from asthmatics to cells of controls. The muscarinic receptor inhibitor tiotropium alone reduced the secretion of IL-6 and IL-8 by fibroblasts. Tiotropium (10-8 M) almost completely blocked the IL-1β-induced IL-6 and IL-8 secretion. Our data indicate that tiotropium reduces an inflammatory response of lung fibroblasts elicited by muscarinic receptors. These data may provide a rationale for the beneficial effects of tiotropium in the treatment of asthma. Supported by: Boehringer-Ingelheim Pharma and the Swiss National Foundation.

91. Lung cell biology

P762
Late-breaking abstract: Differential expression profiles of genes involved in oxidative stress and inflammation in blood and sputum from healthy subjects and COPD patients
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Background: Environmental (mainly cigarette smoke) and genetic factors are known to be involved in the development of chronic obstructive pulmonary disease (COPD); however, a better understanding of the COPD genes expression dysregulation remains a major challenge.

Increased oxidative stress is thought to be central in COPD pathogenesis and directly involved in local and systemic inflammation.

Methods: We have investigated, by RT-PCR array, the mRNA expression profile of 95 genes involved both in inflammation and oxidative stress in sputum and blood from COPD patients (n = 18) and healthy controls (n = 17). We have used Ingenuity Pathway Analysis Software (IPA) to identify the networks of interactions, the biological processes and pathways in which genes showing a significant expression modification are involved.

Results: In the blood cells of COPD, around half of genes showed modifications (26 up and 19 down-regulated) compared to healthy controls and these were essentially involved in inflammation. Using IPA, we found that the most important cellular function altered was the cellular movement. In sputum cells, only 13 genes showed modifications (6 up and 7 down-regulated), five were related to inflammation with blood), most of them being involved in free radical scavenging and cell death.

Conclusions: Compared to healthy subjects, there was a clear dysregulation in gene expression at systemic level, and to a lesser extent, at airway level. Therefore, gene expression profile shows differences between local and systemic compartments.

P763
Late-breaking abstract: Cyclooxygenase- and lypoxigenase-dependent generation of omega-3 electrophilic fatty acid-derivatives with anti-inflammatory properties
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Chronic obstructive pulmonary disease (COPD) is characterized by persistent inflammation of the airways and extensive oxidative damage. Activated macrophages and neutrophils are elevated in the airways of COPD patients where they sustain the inflammatory response and contribute to tissue damage. During inflammatory reactions arachidonic acid (AA) is released from cell membranes and is converted into the pro-inflammatory prostaglandins and leukotrienes by the action of

125s

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cyclooxygenase-2 (COX-2) and lipoxygenases (LO). It has been recently discovered that COX-2 and LO are able to convert alternative substrates, such as the omega-3 docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA), into mediators that actively repress the inflammatory reactions and promote the resolution of inflammation. Herein we report the formation of new omega-3 electrophilic fatty acid derivates by the action of COX-2 and LO in activated human macrophages and stimulated neutrophils. These compounds displayed cytoprotective and anti-inflammatory actions measured as repression of pro-inflammatory enzimes and cytokines and activation of the Nrf2-dependent anti-oxidant response.

Data presented herein strongly suggest that electrophilic derivatives of omega-3 fatty acids are generated in inflamed airways of COPD patients where they may contribute to limit tissue damage and inflammatory processes.

**P764** Late-breaking abstract: Surfactant protein D (SP-D) as a biomarker for mortality: A study in elderly Danish twins

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**Background:** SP-D is synthesized and secreted into the airspaces of the lung by alveolar type 2 pneumocytes and bronchiolar epithelial cells. Specific measurements of SP-D have previously demonstrated to predict survival in patients with idiopathic pulmonary fibrosis and ALI/ARDS. However, SP-D may be a general indicator of pulmonary health and associate to mortality in the general population.

**Aim:** To investigate the association between higher serum SP-D levels and mortality in normal Danes.

**Methods:** A total of 689 twins (234 males and 455 females) provided blood samples during a six month period in a survey (LSADT) performed in 1997. During a 13-year follow-up period 181 (77%) men died and 292 (64%) women died. SP-D serum levels were measured by ELISA technique.

**Results:** Surfactant Protein D levels were positively and significantly correlated to mortality in females. At the end of January 2010, there were 84 male twin pairs (39 MZ and 45 DZ) and 160 female twin pairs (73 MZ and 87 DZ) in which at least one twin had died. There was no evidence of an association between increasing intra-pair difference in log transformed SP-D and mortality in males. In contrast, intrapair analyses in females showed that the twin with the highest SP-D level had a lower risk of death than the co-twin (OR=0.46 vs 1.72; p=0.001). Adjusted Cox regression analysis with intrapair difference in smoking (packyear) and BMI did not affect this association (OR=1.75; p=0.040).

**Conclusions:** These data suggest that circulating SP-D levels may be a biomarker to predict the pulmonary health status and to forecast mortality in the elderly women.

**P765** Late-breaking abstract: Lung regional differences in tissue adaptation to chronic hypoxia (CH)

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Hypoxia (H) impacts to all body tissues which have to adapt to a decrease in O2 delivery. In CH, 10% O2 for 3 weeks) two lung regions from rats, the upper and the lower lobe, showed differences in interstitial tissue structure (Rivolta, I et al. EJR 2011; 37:943-9). On these samples, where the metabolic needs are linked to topographic adaptations of the two lobes can be accounted for a topographic difference in the level of KGF expression, which has been shown to express in the upper lobe. We conclude that variance in tissue structure organization of the two lobes can be accounted for a topographic difference in the level of KGF present in normoxia. On this background, differences in the adaptive response to H might be mediated by differential expression of PGC-1α since HIF1α response was equally affected in both lobes. These results represent a breakthrough in the molecular mechanisms of H adaptation understanding, furthermore, this is the first study considering PGC-1α in the hypoxic lung.

**P766** Engineered nanoparticles induce apoptosis of human bronchial epithelial cells

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Engineered nanoparticles are widely used by the industry, however, it is not clear whether they possess a risk on respiratory health. The objectives of our study were to investigate effects of Titanium dioxide (TiO2) and multi walled carbon nanotubes (MWCNT) on bronchial epithelial cell (BEC) viability and death. BEAS-2B cells and primary BEC obtained from both smokers and patients with COPD were incubated with 0.300 μg/ml TiO2 and MWCNT for 24-48hrs. Cell viability was assessed by MTT, and apoptosis was analyzed by flow cytometry using Annexin V-PE and 7AAD dyes. TiO2 significantly decreased the viability of BEAS-2B cells at 100 (optimal density [OD]=0.65; p=0.001) and 300 μg/ml (OR=0.45; p<0.0001) concentrations after 24hrs as compared control cells (OD=0.85). Similarly, 100 and 300 μg/ml MWCNT decreased viability of these cells following 24 and 48hrs' incubation. Although 300 μg/ml TiO2 induced the viability of primary BEC of smokers (OD=2.15 vs OD=1.52; p<0.0001), 300 μg/ml suppressed cell viability (OD=1.02; p<0.0001) after 24hrs. TiO2 did not change the viability of BEC of COPD patients after 24hrs, whereas 300 μg/ml decreased viability of these cells (OD=0.46 vs 1.72; p=0.001) following 48hrs. Flow cytometry studies of BEAS-2B cells demonstrated that TiO2 (300 μg/ml) decreases percentage of viable cells (90.66% vs 94.01%; p=0.0009), while inducing the percentage of late apoptotic (0.72% vs 4.2%; p=0.017) and necrotic (0.63% vs 4.03%; p=0.0099) cells. MWCNT also showed similar effects on apoptosis of BEAS-2B cells. These findings suggest that engineered nanoparticles may possess a risk on respiratory health by modifying viability and apoptosis of bronchial epithelial cells.

**P767** IL-17 enhances IL-8 production by attenuating both the ARE-mediated and the microRNA-mediated degradation of IL-8 mRNA

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**Background:** IL-17 is a cytokine implicated in chronic inflammation. Enhanced amounts of IL-17 have been found in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD). Previously, we showed inducible IL-17 blockade by anti-IL-17A antibodies did not prevent IL-17 induced IL-8 and IL-6 production in human lung epithelial cells, predominantly by stabilizing IL-6 and IL-8 mRNA. Aim: IL-6 and IL-8 mRNA contains AU-rich elements (ARE) in the 3'UTR, target these mRNAs for facilitated degradation. This decay pathway may be mediated by AU-binding proteins (AU-rips) and possibly microRNAs (miRs). We have assessed whether AU-rips (TTP, KHSRP, AUF1) and/or miRs are involved in IL-8 mRNA degradation. And, if so, whether IL-17 modulates these pathways.

**Results:** Inhibition of miR16, or knock-down of TTP or KHSRP resulted in a marked increase of TNF-a-induced IL-8 production, which was paralleled by stably increasing IL-8 mRNA degradation. Conversely, knock-down of AU-1 reduced IL-8 mRNA expression and promoted degradation of IL-8 mRNA. IL-17 halts IL-8 mRNA degradation by enhancing the role of AUFI1 which protects IL-8 mRNA from degradation. Furthermore, IL-17 reverses the TNF-a-induced production of miR16.

**Discussion:** These findings strongly indicate that IL-17 enhances IL-8 production by attenuating two pathways that degrade IL-8 mRNA. We have obtained similar data for several other inflammatory mediators. Since airway epithelial cells from patients with asthma display enhanced IL-8 production we are assessing whether there is an intrinsic disturbance in these mRNA decay pathways.

This work is supported by the Netherlands Asthma Foundation (3.2.06.031).

**P768** A quantitative method for the detection of spliced X-box binding protein 1 (XBP1) mRNA in primary bronchial epithelial cells (PBEC) as a measure of endoplasmatic reticulum (ER) stress

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Accumulation of unfolded or misfolded proteins in the ER can cause ER stress, which is increasingly seen in diseases such as cystic fibrosis, alpha-1-antitrypsin deficiency and Alzheimer disease. ER stress leads to the activation of the unfolded protein response (UPR). UPR signaling involves splicing of XBP1 mRNA and induction of gene expression by the transcription factors CHOP, which is a key-signaling component of ER-stress induced apoptosis. In present studies, XBP1 splicing is frequently used as an important marker for ER-stress and is visualized by gel electrophoresis which is laborious and difficult to quantify. The aim of this study was to develop and validate a quantitative RT-PCR (qPCR) which detects only the spliced form of XBP1 mRNA. We stimulated PBEC with thapsigargin and tunicamycin, both known ER-stress inducers, and performed qPCR with primers that were designed to recognize only the spliced form of XBP1. We also performed qPCR for CHOP and BIP and correlated this with
P769
Pulmonary apoptosis in fetal Down syndrome

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Background: Increased levels of apoptosis have been implied in various non-
 pulmonal conditions frequently found in Down syndrome (DS). Children with
 DS are at increased risk for acute lung injury and fetal lung development is 
disrupted in DS. In both processes, apoptosis plays a key role. Nevertheless, 
pulmonary apoptosis has not been studied in DS.

Aim: We hypothesized that the amount of apoptotic epithelial cells in fetal lungs of 
DS is increased compared to controls.

Methods: We compared lung tissue sections from autopsies of 21 fetuses with 
DS and 12 controls (16-24 weeks gestational age (GA)). Sections were double 
stained with antibodies against pan-cytokeratin (CK) and activated caspase-3 (C3), 
markers for epithelium and apoptosis. Per section, 7 random photographs were 
taken at 200x magnification. Spectral imaging software was used to quantify the 
mean number of pixels that showed colocalization of CK and C3. All sections were 
H&E stained to determine the presence of canalicular or sacular morphology.

Results: The mean (SD) percentage of CK-positive pixels was equal between DS 
and controls (27.2% (4.7) versus 27.1% (6.2), p=0.97). The median percentage 
(IQR) of C3-positive pixels that showed colocalization of C3 was 0.16% (0.18) 
in DS compared to 0.27% (0.24) in controls (p=0.45). This was independent of 
the induction of CHOP and BiP was r=0.962 (p<0.000), respectively. We compared the new method with the visualization of the spliced 
XBP1 mRNA to validate the results. The spliced XBP1 PCR product from a control 
was investigated by qRT-PCR, western blotting and immunohistochemistry using 
the catalytic subunit of γ-GCS and GR (glutathione reductase) mRNA.

Conclusion: The number of apoptotic epithelial cells in lungs of DS fetuses does 
not differ from controls. We did find a difference in the development of epithelial 
structures and acinar development. This might explain anomalies in alveolar 
development found at birth in DS.

P770
Airway epithelial protocadherin-1 expression is regulated by house-dust mite 
cigarette smoke exposure in mice

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Recently, we identified Protocadherin-1 (PCDH1) as a novel susceptibility gene for 
Bronchial Hyperresponsiveness (BHR). PCDH1 is expressed in airway epithelial 
cells and encodes two isoforms of a protocadherin transmembrane protein. We aim 
to get insight into PCDH1 function in airway epithelial cells in relation to BHR. 
Therefore, we analyzed in vivo regulation of Pcdh1 isoforms in lungs under basal 
conditions and in mouse models of short-term cigarette smoke (CS) exposure and 
house-dust mite (HDM) driven experimental asthma. Pcdh1 gene-structure was 
investigated by Rapid Amplification of cDNA Ends (RACE). Pcdh1 expression 
was investigated by qRT-PCR, western blotting and immunohistochemistry using 
isoform-specific antibodies.

We identified a novel isoform of Pcdh1 lacking the transmembrane domain but re-
taining the intracellular signalling motifs, indicating a novel function as signaling 
adaptor molecule. Bronchial epithelial cells expressed all isoforms of Pcdh1, while 
airway smooth muscle only expressed the isoforms encoding the signal transduction 
domains. Surprisingly, Pcdh1 expression was unaffected during HDM-exposures, 
but increased after termination of the treatment, indicating a putative role in ep-
ithelial repair. In strong contrast, Pcdh1 mRNA expression was markedly reduced by 
CS exposure, as soon as 6 hours after a single exposure. These latter data are 
especially of interest given the initial identification of linkage to the PCDH1 
region in CS-exposed families. We conclude that CS-induced changes in airway 
epithelium directly affect Pcdh1 expression levels, and hypothesize that PCDH1 regulation contributes to the epithelial response to CS-induced injury.

P771
Fluticasone furoate restores leptin/leptin receptor pathway in nasal 
epithelial cells

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Leptin/leptin receptor pathway has been shown to be involved in the epithelial 
homeostasis and in tissue repair. Allergic rhinitis (AR) is characterized by a 
highly mediated inflammation induced by the allergen exposure, leading to a chronic 
inflammation with consequential structural abnormalities in the nasal epithelium. 
Topical corticosteroids are recommended as first-line therapy in AR. The role 
of the leptin/leptin receptor pathway and the specific effects of fluticasone furoate 
(FF), a new topical corticosteroid, in the homeostasis of nasal epithelial cells are 
largely unknown. We aimed to determine whether a nasal epithelial dysfunction of 
leptin/leptin receptor pathway contributes to AR pathogenesis and to investigate 
the effect of FF on this pathway. The human nasal epithelial cell line RPMI 2650 
was first examined for leptin/leptin receptor expression by immunocytochemistry 
and by flow-cytometry. Then, the RPMI 2650 cells were cultured in the presence 
or absence of the allergen extract birchiana judaica (PAR1), of the fibrogenic 
cytokine TGF-β1 and of FF and analyzed for leptin receptor by flow-cytometry 
and for cell proliferation by clonogenic assay. The RPMI 2650 cells express leptin 
receptor. PAR1 and TGF-β1 significantly decreases the leptin receptor 
expression and cell proliferation and FF completely abolishes and reverts the 
effects of both PAR1 and TGF-β1. In conclusion, allergen exposure and TGF-β1 
alter the homeostasis of nasal epithelium by down-regulating leptin/leptin receptor 
pathway whereas FF is able to restore both this pathway and nasal epithelial 
homeostasis.
Results: Basal production of IL-8 by mitochodrially impaired AS49.B2 cells is increased compared to AS49 control cells. Moreover, suppression of IL-8 by the GC budesonide (10-8M) is significantly less (24%±6%, p=0.02) in AS49.B2 cells compared to AS49 cells. Furthermore, while budesonide was able to efficiently increase barrier function in control AS49 cells (p<0.001), there was not significant effect in AS49.B2 cells. Finally, we observed that AS49.B2 cells were less capable to recover from wound than control AS49 cells.

Conclusion/Discussion: In conclusion, our data indicate that mitochondrial dysfunction leads to increased pro-inflammatory activity, inefficient wound healing and reduced responsiveness to GCs. We speculate that mitochondrial dysfunction as observed in COPD may contribute to the GC-insensitive chronic airway inflammation in this disease.

P774
Effect of phosphodiesterase IV inhibitors on eotaxin expression in bronchial epithelial cells – Comparison between immortalized and primary line
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Eotaxins are an important agents of the patophysiology in the obstructive airway diseases. They are responsible for eosinophil recrutation into respiratory tract. Phosphodiesterases (PDEs) are a huge and diversified family of enzymes decomposing cAMP. PDE4 inhibitors as drugs, act through cAMP elevation and can inhibit inflammation in many ways. The aim of this work was to evaluate the effect of PDE4 inhibitors (rolipram and RO-20-1724) on eotaxin (CCL11, CCL24 and CCL26) expression in human bronchial epithelial cells: immortalized - BEAS-2B (ATCC) and primary (ATCC). Cells were preincubated with PDE4 inhibitors for 1 h and stimulated with IL-13. TNF-α or IL-13+TNF-α for 48h. Protein levels were measured using ELISA kits, changes in genes expression were measured using real time PCR.

Results: The both of cell lines produced different eotaxins: BEAS-2B synthesized CCL11 and CCL24, BEHC – CCL11 and CCL26. Distinct effects of PDE4 inhibitors in hBECs in immortalized as compared to primary cell line were observed. PDE4 inhibitors decreased the level of eotaxin gene and protein expression in BEAS-2B usually in statistically significant manner. PDE4 inhibitors stimulated eotaxin gene expression; specially rolipram significantly increased the mean levels of eotaxin expression, but did not change their protein synthesis.

Conclusions: The data do not permit to suggest the effect of PDE4 inhibitors on bronchial epithelial cells because of the differences in the biology of the both used cell lines. Unequivocal resoluction of the problem needs more experimental trials using more primary cell lines or experimental animal model.

P775
ciliaFA: A free research tool for accurate, automated, high-throughput measurement of ciliary beat frequency (CBF)
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Aim: To develop a program that allows batch processing of multiple movie (.avi) files for measurement of CBF.

Introduction: A program was developed that converts average pixel intensities within a region of interest to a waveform. The waveform is analysed by fast fourier transform (FFT) to extract the dominant frequency. The code runs on freeware and cell proliferation in primary human lung fibroblasts (n=6).

Methods: Image files of 115 ciliated epithelial cell cultures were captured using a digital high-speed video recorder. In order to capture a range of CBF measurements, the bacterial toxin, pneumolysin, was used to inhibit CBF. Mean CBF was measured by conventional frame by frame counting of ciliary beat cycles by slow motion playback were compared with those obtained using the automated ciliaFA system.

Results: The mean (sd) difference between the ciliaFA and conventional methods was -0.4 (1.6) Hz, the correlation coefficient was shown to be 0.8 and the Bland-Altman limits of agreement were -3.5 to 2.7 Hz.

Conclusion: The data showed that the ciliaFA software calculated consistent CBF measurements. The advantages of this system include automated, high throughput CBF analysis; whole field and individual region of interest measurements, and elimination of selection bias.

P776
Interactions between epithelial cells and neutrophils during pro-inflammatory conditions
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Inter-cellular communication is essential for defense and survival of the organism. The aim of the study was to find out whether there is an active cross-talk between cells constituting the first line of defense; alveolar epithelial cells (AS49) and neutrophils, following activation with pro-inflammatory stimuli in vitro. Further, to explore whether this communication is altered in chronic obstructive pulmonary disease (COPD), a condition characterized by chronic airway and lung inflammation.

Primary neutrophils from healthy subjects and COPD-patients were co-cultured with AS49 cells in medium and in medium containing lipopolysaccharide (LPS), peptidoglycan (PGN) or tumor necrosis factor (TNF). The expression of TL2R, TL4 and CD14 on the cell surface of neutrophils was assessed by flow cytometry and CXCL8 (IL-8) and soluble CD14 (sCD14) in the supernatant were measured with ELISA.

On neutrophils, the surface expression of TL2R was diminished following activation with all three pro-inflammatory stimuli and membrane bound (sCD14) and TL4 expression were increased in co-cultures compared to single cell cultures, irrespective of pro-inflammatory stimulation. A strong correlation between CXCL8 and sCD14 was observed in LPS-stimulated co-cultured cells.

These data showed a down regulation of TL2R on neutrophils induced by pro-inflammatory stimuli and is strongly suggesting an active cross talk between AS49 cells and blood neutrophils, both in unstimulated cells and following activation with pro-inflammatory stimuli, in vitro.

P777
Effect of cigarette smoke extract or TGF-β1 on hyaluronan production and hyaluronan modulating enzymes in primary murine lung fibroblasts
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Hyaluronan (HA) is a component of the extracellular matrix and low molecular weight (LMW) HA fragments have pro-inflammatory capacities. Exposing mice to cigarette smoke (CS) for 1 or 6 months results in enhanced deposition of LMW HA in lung parenchyma and airways walls and in altered expression of HA syntheses and hyaluronidases (Bracke et al., Am J Respir Cell Mol Biol. 2010;52(6):753-61). To pinpoint a source of HA, we studied HA-production and HA modulating enzymes in primary murine pulmonary fibroblasts stimulated with cigarette smoke extract (CSE) or TGF-β1.

Fibroblasts were isolated from lungs of C57BL/6 mice and cultured in vitro. At passage 6, cells were stimulated with 24h or 48h with control medium, 5% CSE or 2ng/ml TGF-β1. mRNA expression of HA syntheses (Has1, Has2, Has3) and hyaluronidases (Hyal1, Hyal2) was evaluated by RT-PCR. HA production was measured in supernatant by ELISA.

In vitro stimulation of pulmonary fibroblasts with CSE significantly decreased the mRNA expression of Has1 (synthesizing high molecular weight (HMW) HA) and significantly increased the expression of Hyal2 (degrading HMW HA to LMW HA fragments). Stimulation with TGF-β1 resulted in significantly increased mRNA expression of Has2 (synthesizing HMW HA). Accordingly, HA-levels in the fibroblast supernatant decreased significantly upon 48h stimulation with CSE, while they were significantly increased upon 24h or 48h stimulation with TGF-β1.

Decreased Has1 and increased Hyal2 in CSE-stimulated fibroblasts suggests reduced synthesis and enhanced breakdown of HMW HA. This may contribute to the accumulation of LMW HA fragments, observed in CS-exposed mice.

P778
Cigarette smoke down-regulates the expression of β-catenin in primary human lung fibroblasts
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Rationale: Cigarette smoke is the major cause of COPD/emphysema but the etiology of these diseases is still unknown. β-catenin is a signalling molecule which is regulated through degradation/stabilization mechanism, and which promotes cell proliferation via the Wnt signaling pathway. Decreased β-catenin signaling may be involved in the parenchymal tissue destruction leading to emphysema.

Objectives: Investigate the effect of cigarette smoke on the expression of β-catenin and cell proliferation in primary human lung fibroblasts (n=6).

Methods: Fibroblasts were exposed to cigarette smoke conditioned medium (20%,
P779 Anti-inflammatory effect of beclomethasone dipropionate and formoterol on TNF-α-induced human endothelial cell activation
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To investigate the effect of beclomethasone dipropionate (BDP) and formoterol (F), either alone or in combination, on TNF-α-induced ICAM-1 expression and IL-8 release in human umbilical vein endothelial cells.

Methods: Cells were incubated with BDP (10^{-11} - 10^{-5} M), F (6/100 with respect to BDP concentration) or drug diluent (control cells: CC) and then exposed to TNF-α (200 U/ml; 4 hrs). For BDP/F combination (n=10/8/6), EC were treated with low doses of BDP (10^{-10} and 10^{-8} M) and/or F (6×10^{-5}-6×10^{-3} M). Surface ICAM-1 expression and IL-8 release were measured by ELISA.

Results: BDP reduced TNF-α-induced IL-8 release (mean±SEM; 5.6±0.5 fold; p<0.05 vs CC); F did not significantly affect IL-8 release (9.2±0.8% at the maximal dose tested). In a different experimental set, BDP/F inhibited IL-8 release with respect to TNF-α alone (10^{-9}M×6×10^{-5} M; 27.6±3.4 vs 10^{-3} M 14.6±3.5%; p<0.05 vs CC), achieving an effect comparable to that observed with BDP 10^{-9} M alone; BDP/F, though to a less extent, tended to decrease ICAM-1 expression (10^{-9}M×6×10^{-5} M; 17.2±6.8 vs 10^{-5} M 9.3±2.1%; and F=4±2.6; p=0.05, n=5).

Conclusions: BDP in combination with F is more effective in inhibiting EC activation as compared with BDP alone, thus allowing to use lower BDP doses to reach the maximum inhibitory effect. These results may explain some clinical anti-inflammatory activities of BDP/F combination.

92. The ageing pulmonary interstitium

P780 Ambrisentan attenuates lung and heart injury in a rat model of bronchopulmonary dysplasia
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The selective endothelin receptor type A antagonist ambrisentan may be a novel therapeutic agent in neonatal chronic lung disease by blocking the adverse effects of the potent vasconstrictor endothelin-1, including pulmonary arterial hypertension (PAH)-induced right ventricular hypertrophy (RVH). The cardiopulmonary effects of ambrisentan were studied in neonatal rats with hyperoxia-induced lung injury. Ambrisentan treatment was investigated in 2 models of experimental BPD: a prophylactic model, in which pups were continuously exposed to hyperoxia and treated daily with either saline or ambrisentan (20 mg/kg body weight/day); and an experimental model, in which pups were exposed to hyperoxia for 9 days, followed by 9 days of recovery in room-air and treatment with ambrisentan was started on day 6 of oxygen exposure and continued during the recovery period. In the prophylactic model treatment with ambrisentan improved survival (p<0.01) by reducing lung fibron deposition (3-fold, p<0.001), alveolar septum thickness (1.7-fold, p<0.001) and alveolar wall thickness of small arteries (3-fold, p<0.01), and preventing associated RVH (p<0.001). Treatment with ambrisentan did not have beneficial effects on alveolar enlargement, vascularization, the pulmonary influx of macrophages and neutrophils, and the mRNA expression of procollagant and inflammatory markers. In the injury-recovery model treatment with ambrisentan attenuated PAH and RVH (p<0.001), demonstrating that established PAH-induced RVH is still reversible in the adult period. Beneficial effects on reduced pulmonary vascularization and alveolarization were absent.

P781 Serum HSPI74 is a novel blood marker for rapidly progressive interstitial pneumonia
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Heat shock protein (HSP) 47, a collagen-specific molecular chaperone, is involved in the processing and/or secretion of procollagen. The aim of this study was comparative analysis of the diagnostic values of serum HSPI74. Krebs von den Lungen-6 (KL-6), surfactant protein (SP) A, SP-D and lactate dehydrogenase (LDH) levels for rapidly progressive interstitial pneumonia. Subjects comprised 27 patients with rapidly progressive interstitial pneumonia, 12 with cryptogenic organizing pneumonia (COP), 19 with idiopathic usual interstitial pneumonia (UIP), 16 with idiopathic nonspecific interstitial pneumonia (NSIP), 11 with collagen vascular disease-associated UIP, 11 with collagen vascular disease-associated NSIP, and 18 healthy adult volunteers. Serum levels of HSPI74 in patients with rapidly progressive interstitial pneumonia were significantly higher than those in patients with COP, idiopathic UIP, idiopathic NSIP, collagen vascular disease-associated UIP, collagen vascular disease-associated NSIP, and healthy adult volunteers. Receiver operating characteristic curves revealed that HSPI74 was superior to the other markers. The cut-off level for HSPI74 that resulted in the highest diagnostic accuracy was 809.6 pg/ml. The sensitivity, specificity, and diagnostic accuracy were 92.9%, 100%, and 98.2%, respectively. These results suggest that of the markers studied, HSPI74 is the best serum marker for rapidly progressive interstitial pneumonia.

P782 Protease-activated receptor-2 triggers epithelial to mesenchymal transition: Potential relevance in pulmonary fibrosis
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Idiopathic pulmonary fibrosis (IPF) constitutes the most devastating form of fibrotic lung disorders. The destructive fibrotic focci characteristic of IPF originate, at least partly, via epithelial to mesenchymal transition (EMT). The extracellular signals and cellular receptors triggering EMT in IPF remain incompletely understood however. Recently, we showed that protease-activated receptor-2 (PAR-2), a transmembrane G-protein-coupled receptor expressed ubiquitously in the lung, is an essential player in fibrotic lung disorders by directly targeting fibroblasts. Here, we explore the role of PAR-2 on epithelial cells by focussing on PAR-2-induced EMT in pulmonary fibrosis. Immunostaining of lung biopsies of IPF patients showed prominent PAR-2 expression by fibroblasts and epithelial cells overlying fibrotic focci. Double stainings indicated that PAR-2 co-localized on cells expressing both epithelial (cytokeratin) and mesenchymal (vimentin) markers, indeed suggesting a role of PAR-2 in EMT in IPF. Subsequent in vitro experiments showed that PAR-2 stimulation induced a fibroblast-like morphology in type II lung epithelial cells, the expression of the myofibroblast markers vimentin and α-SMA, and the secretion of collagen. Interestingly, PAR-2 stimulation triggered β-catenin accumulation and translocation to the nucleus. In conclusion, PAR-2 triggers EMT of epithelial cells and PAR-2 dependent activation of the β-catenin/WNT signaling pathway is probably the main driver of PAR-2-induced EMT. Overall our data thus suggest that inhibition of the PAR-WNT axis may be a clinically relevant treatment option in IPF but also in other disorders in which EMT is essential.

P783 Disruption of Nrf2 enhances susceptibility to pulmonary fibrosis induced by bleomycin in mice
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NRF2 is one of the main transcription factors regulating the expression of phase II genes. Stimulation of Nrf2 by antioxidants and drugs strongly improves survival in bleomycin fibrosis. Moreover, we showed that NRF2 is involved in the expression of several pro-collagen V genes and fibroblasts. However, the role of NRF2 in fibroblasts is still unknown. To explore whether NRF2 enhances or suppresses EMT mediated by PAR-2, we generated NRF2−/− mice and compared bleomycin induced fibrosis in NRF2−/− and NRF2+/+ mice. NRF2−/− mice showed significantly increased lung inflammation, fibroblast proliferation, fibroblast got a more fibroblast-like morphology, and increased protein expression of a-SM-A and collagen type 1. In conclusion, NRF2 enhances susceptibility to bleomycin-induced pulmonary fibrosis.
Introduction: Recent studies suggest that N-acylcycteine improve the idio-
pathic pulmonary fibrosis. Oxidant/antioxidant balances may play an important
role in many of the processes of inflammation and fibrosis. Nrf2 is involved in the trans-
scriptional regulation of many antioxidant genes. We therefore investigated the
role of Nrf2 against the development of pulmonary fibrosis in mice.

Materials and methods: Both Nrf2+/- and Nrf2–/– C57BL/6J mice were used. Bleo-
mycin was administered intravenously to the mice at a dosage of 0, 70, 80, and
90 mg/kg body weight on day 0, and the fibroblastic foci were assessed histo-
logically by Ashcroft score determined in the lung tissues on day 28. Furthermore,
bleomycin was administered intravenously to the mice at a dosage of 0, 70, 80,
and 90 mg/kg body weight on day 0, and the bronchoalveolar lavage (BAL) fluid examined for
cell populations on days 0, 3, 7, 10, 14, 21, and 28.

Results: The fibroblastic foci were induced by bleomycin at a dosage of 90mg/kg
body weight on day 14 in both Nrf2+/- and Nrf2–/– mice. The total number of cells and macrophages in the BAL fluid were
significantly increased from day7 after bleomycin administered in both Nrf2+/-
and Nrf2–/– mice. The increased cells number were significantly greater in Nrf2+/-
mice than in Nrf2–/– mice.

Conclusions: These findings suggest that Nrf2 might be an important gene fac-
tor in the determination of susceptibility to bleomycin induced pulmonary fibrosis
by regulating the macrophages defense mechanisms.

P784
αB-crystallin is involved in the process of pulmonary fibrosis
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Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease with
currently no treatment. In the presence of TGF-β, epithelial cells differentiate into
myofibroblasts, key pro-fibrotic cells in a process called epithelial-to-mesenchymal
transition (EMT). αB-crystallin belongs to the small heat shock protein family and is constitutively
expressed in many tissues including lungs. αB-crystallin is inducible by stress
and has a major role in cell cytoskeleton architecture homeostasis by interacting
with intermediate filament elements. The role of αB-crystallin in fibrogenesis is unknown.

Methods: In vitro we induced EMT on A549 cells after TGF-β treatment. In vivo,
Sprague Dawley rats received intra-tracheal administration of AdTGF-β or Ad
empty vector. In these experiments, wild type (WT) or knock out (KO) for
αB-crystallin received intra-tracheal bleomycin (0.07U/mouse).

Results: In vitro during TGF-β1 induced EMT: 1. αB-crystallin is early overex-
pressed, 12 hours before α-SMA overexpression; 2. αB-crystallin colocalize with
α-SMA; 3. αB-crystallin interacts with HSP72/74. The modulation of αB-crystallin plays a role on TGF-SMAD pathway.
In vivo: 1. αB-crystallin is overexpressed in fibrotic areas induced by TGF-β overexpression in rats or bleomycin administration in mice. 2. By day 21, collagen accumulation in the lung was significantly higher in WT mice (3 fold increase, p<0.05) compared to KO mice; 3. The level of TGF-β1 was lower in KO mice after bleomycin injection.

Conclusion: These results provide evidence that αB-crystallin is involved in
pulmonary fibrosis maybe through a role in EMT.

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P785
Systemic sclerosis patients’ sera recognize collagen V in experimental
scleroderma lung fibrosis
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Background: Type V collagen (COLV) has been recognized as an auto antigen
involved in lung transplantation rejection and may be involved in systemic scle-
rosis pathogenesis (SSc), since immunization of healthy rabbits with this collagen
induced an experimental model with similar characteristic of SSc patients.

Objective: To investigate if SSc patient’s sera recognize COLV present in pul-
monary tissue from this model and collagen isolated from supernatant culture of
pulmonary fibroblasts from these patients.

Methods: Immunofluorescence using collagen type I, III and IV adsorbed sera
from 8 SSc treatment naive patients and from 8 controls was performed to evaluate
COLV reactivity in lung tissue from experimental model. These sera were also
tested by immunoblotting to evaluate COLV reactivity in collagen isolated from
SSc patient’s lung fibroblasts supernatants.

Results: Positive immunofluorescence reaction was observed when the sera of
SSc patients recognized epitopes of COLV in the experimental model vessels walls
and pulmonary interstitium contrasting with the negative reaction observed in

the control. Morphometric analysis confirmed these findings, demonstrating a
higher COLV reactivity to sera from SSc patients when compared to the control
P<0.0028). Immunoblotting showed that SSc patients sera strongly reacted to
COLV standard and to the high molecular weight (fragments of COLV isolated
from SSc lung fibroblasts culture supernatants, different from control sera reactivity
(P<0.02).

Conclusions: SSc patient’s sera recognize COLV epitopes in experimental model
lung tissue and SSc patient’s lung fibroblasts culture supporting that this protein is
an antigen involved in SSc pathogenesis.
P788 Enhanced acute pulmonary inflammation and reduced fibrotic response in quartz-exposed p47phox-deficient mice

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Previous studies have shown that quartz (crystalline silica) provides a useful tool to study experimental fibrosis in rodents. In the present study, we have investigated the involvement of-phagocyte-derived reactive oxygen species (ROS) in quartz-induced inflammatory and fibrotic responses. NADPH oxidase p47phox subunit deficient mice and their wild type counterparts were exposed to 100 mg/kg b.w. quartz via a single pharyngeal aspiration. After 24 hours markers of myofibroblast and oxidative stress were investigated in bronchovascular lavage fluid (BALF) and lung tissue. Quartz elicited a strong acute inflammatory response, characterized by a remarkably similar pulmonary influx of neutrophils in both strains. Interestingly, however, luminescence multiple-analysis of BALF revealed stronger increases of interleukin (IL)-1β, IL-6, keratinocyte-derived chemokine (KC), monocyte chemotactic protein-1 (MCP-1) and granulocyte colony stimulating factor (G-CSF) in the knockout mice compared to wild type animals. Differences in IL-4, IL-10, IL-13 and tumour necrosis factor-alpha (TNF-α) were not detectable. In contrast, pulmonary mRNA levels of the oxidative stress markers NADPH oxidase 4 (NOX4) and NADH-oxidase 1 (NOX1) were significantly enhanced only in the wild type mice in response to quartz treatment. Three months after quartz treatment, significantly less fibrosis occurred in the lungs of knockout mice, as indicated by hydroxyproline content and Masson’s trichrome staining. These data show that impairment of NADPH oxidase increases acute inflammatory responses, whereas it reduces oxidative stress and fibrosis in the lungs of quartz-exposed mice.

P789 Muscarinic receptor stimulation differentially regulates extracellular matrix gene expression in lung fibroblasts

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Airway fibrosis is a characteristic feature of both asthma and COPD, in which fibroblasts are importantly involved. Increased activity of the cholinergic system may contribute to airway fibrosis, as muscarinic receptor stimulation has been shown to enhance collagen deposition by fibroblasts. The effects of muscarinic receptor stimulation on the expression profile of other extracellular matrix (ECM) proteins, however, remains to be established. To assess the effects of muscarinic receptor stimulation on ECM gene expression, human lung fibroblasts were exposed to 100 μM of the muscarinic receptor agonists methacholine and carbachol in the presence of the fibroblast growth factor TGFB-1 (2 ng/ml), after which ECM gene expression was determined by quantitative PCR. The results demonstrate that methacholine concentration-dependently enhanced gene expression of the laminin α1 chain, whereas expression of the decorin gene was decreased. No effects of methacholine were observed on the gene expression of collagen I, collagen III, fibronectin, biglycan, versican or laminin α2, β1 and γ1 chains. In the presence of TGFB-1, methacholine (10 μM) enhanced gene expression of fibrillin and collagen I. No additional effects of methacholine were observed on the expression of the other ECM genes investigated. Collectively, these results indicate that muscarinic receptor stimulation selectively changes the expression of specific ECM genes, which may contribute to the airway remodelling as observed in asthma and COPD.

P790 Collagen V and decorin is involved in systemic sclerosis pulmonary fibrosis

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Background: Systemic sclerosis (SSc) is characterized by vasculopathy, inflammation, autoimmunity and fibrosis. Collagen V (COLV) is involved in SSc since increased amount of unusual COLV in SSc lung patients indicating a role for this protein. We evaluated COLV and decorin expression and tridimensional reconstruction of fibroblasts culture used quantitatively.

Methods: We evaluated COLV and decorin expression and tridimensional reconstruction by immunofluorescence in SSc patients without pulmonary hypertension that underwent surgical lung biopsy (n=6) and healthy controls from trauma (n=6). Biochemical characterisation of COLV from lung fibroblasts culture used quantitatively.

Results: COLV fibers was distorted and thickened in SSc lung tissue compared to thin fibers of controls. Decorin was distributed around COLV fibrils in the bronchovascular interstitium and vascular walls. Histomorphometric analysis of SSc demonstrated increased expression of COLV in group B (p<0.01) and decorin (p<0.01) when compared to control. Immunoblotting detected an increased high molecular weight COLV fraction in SSc (p<0.02).

Conclusion: Over expression and unusual organization of COLV fibers with biochemical changes associated to increased decorin indicates that matrix signalization pathway is involved in COLV fibrogenesis process in SSc pulmonary fibrosis.

P791 The effect of erythropoietin (EPO) on collagen type-2 (COL-2) and cytokrome-c (CYT-c) in the bleomycin (BLM)-induced pulmonary fibrosis (PF) in rats

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Purpose: The enzymes COL-2 and CYT-c are known to be a part of the fibrictic pathway. EPO is a multiple functional cytokine with anti-inflammatory and anti-apoptotic properties. Aim of this study was to investigate the role of EPO on the expression of both enzymes in BLM-induced PF in rats.

Methods: Fifty Wistar rats (300gr) were divided into five groups of 10 animals each: 1)control animals,2)intratracheal (i.t) and intraperitoneal (i.p) injection of bleomycin (0.5mg/kg) i.t injection,3)BLM hydrochloride (7.5mg/kg) i.t injection followed by EPO (1 i.p injection 2000 iu/kg),suladine (0.5mg/kg) i.t injection followed by EPO i.p injection (2000 iu/kg). All rats were necropsied after 14 days. Histomorphometric evaluation was performed for the expression of COL-2 and CYT-c. A scale of 4 grades was used for the evaluation of the results: 0.25% (A), 25-50% (B), 50-75% (C), 75-100% (D).

Results: In groups 1,2 and 5, both COL-2 and CYT-c were expressed in the grade A (80%) and in the grade B (20%). In group 3, COL-2 was expressed in the high grades B (20%), C (60%) and D (20%), and CYT-c only in the two higher grades. C (70%) and D (30%). In group 4 both enzymes were expressed only in the low grades A (80% and 70% respectively) and B (20% and 30% respectively). The expression of COL-2 and CYT-c took place in the high grades for BLM group and in the lower grades for BLM+EPO group (p<0.001 and p<0.05 respectively).

Conclusions: BLM injection followed by EPO resulted in significant lower expression of COL-2 and CYT-c compared with BLM group. The protective mechanisms of EPO on PF must be further clarified.

P792 Microparticles-associated tissue factor activity is increased in bronchovascular lavage of patients with pulmonary fibrosis and correlates with functional impairment

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Background: The activation of the coagulation cascade plays a role in theogenesis of pulmonary interstitial fibrosis. Furthermore, microparticles (MP) are effective in experimental lung fibrosis and possibly in patients with idiopathic pulmonary fibrosis. Microparticles (MP) are cell derived procoagulant and proinflammatory vesicles that can express tissue factor (TF); MP represent a storage pool of bioactive effectors and are emerging as a new family of physiologically relevant mediators. Aim: To evaluate the presence of TF-bearing MP in the bronchovascular lavage fluid (BALF) of patients with pulmonary fibrosis (PF) in comparison with control patients, and to correlate their concentration with the degree of functional impairment.

Methods: Seven patients with PF and 10 control patients with suspected lung cancer or infectious diseases underwent bronchoscopy. The presence of MP was evaluated through a prothrombinase assay that measures phosphatidylserine (PS) concentration; TF activity was assessed by a one-stage clotting assay.

Results: The BALF of patients with PF had a higher concentration of microparticles (87.23 [67.21-108.8] vs 49.19 [29.50-77.22] nM PS, p<0.05) and a greater TF activity (27144 [1723-29998] vs 8596 [4019-21962] arbitrary U, p<0.05) (data expressed as median [interquartile range]). We found a significant negative correlation between MP-associated TF activity and forced vital capacity% predicted (r²=95, p<0.001 and DLCO% predicted r²=96, p=0.05).

Conclusions: Our preliminary data are consistent with an involvement of TF-bearing procoagulant MP in the pathogenesis of PF and in disease progression.

P793 Study of tetradhydrobiopterin in idiopathic pulmonary fibrosis and COPD

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Introduction: Tetradhydrobiopterin (BH4) is an essential cofactor for the activity
of nitric oxide synthase enzyme (eNOS). Deficiency of BH4 induced by oxidative stress could produce eNOS uncoupling and contribute to pulmonary damage. 

**Objective:** To study the role of endogenous BH4 in patients with stable idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD).

**Materials and methods:** Twenty-eight patients (15 IPF, 13 COPD; 61 (13) years) and 9 healthy controls were studied. Lung function tests (spirometry, plethysmography and lung diffusion capacity), HRCT (High Resolution Computed Tomography) lung scan and 6-min walk test were performed in all patients. Blood neutrophilic, plasma BH4 (reverse-phase high-performance liquid chromatographic (RP-HPLC) with fluorescence detection), hemoglobin, fibrinogen, and CRP were also measured. Differences in BH4 levels between groups and its relationship with clinical, functional or biological parameters of disease severity were analyzed.

**Results:** BH4 was significantly reduced in IPF (1.32 ± 0.16), and COPD (1.44 ± 0.27) patients versus controls (2.42 ± 0.29). There were no differences in BH4 levels between either IPF and COPD or bronchitis and emphysema phenotypes. BH4 levels were not related with parameters of lung function, radiological extension, inflammatory markers or smoking severity. In patients with COPD, BH4 levels were related with the number of previous exacerbations.

**Conclusions:** Plasma BH4 levels are reduced in IPF and COPD, which may be of potential value as a future biomarker of oxidative stress-related diseases.

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**Increase of nitrosative stress in patients with eosinophilic pneumonia**

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**Background:** Exhaled nitric oxide (NO) production is increased in asthma and reflects the degree of airway inflammation. The alveolar NO concentration (Calv) in interstitial pneumonia is reported to be increased compared to that in asthma. However, it remains unknown whether NO production is increased and nitrosative stress occurs in eosinophilic pneumonia (EP).

**Objective:** We hypothesized that nitrosative stress markers including Calv, inducible type NO synthase (iNOS), and 3-nitrotyrosine (3-NT), are upregulated in EP.

**Methods:** Exhaled NO was measured in healthy subjects and in patients with interstitial pneumonia including idiopathic pulmonary fibrosis (IPF), cryptogenic organizing pneumonia, hypersensitivity pneumonitis, sarcoidosis and EP. iNOS expression and 3-NT formation were assessed by immunocytochemistry in BALF cells. The exhaled NO, lung function, and systemic inflammatory markers of the EP were evaluated after corticosteroid treatment.

**Results:** The Calv levels in the EP group were significantly higher than those in the healthy subjects and the other interstitial pneumonia groups as well as the fractional exhaled NO (FeNO) levels. More iNOS and 3-NT positive cells were observed in the EP group compared to the healthy subject and IPF patient. The Calv levels had significant correlations with both iNOS (p < 0.05) and 3-NT positive cells (p < 0.05). Corticosteroid treatment significantly reduced both the FeNO (p < 0.05) and the Calv levels (p < 0.01). The magnitude of reduction in the Calv levels had a significant correlation with the peripheral blood eosinophil counts (p < 0.05).

**Conclusion:** These results suggested that nitrosative stress was augmented in EP and may be involved in the pathogenesis.

P795

**Molecular mechanism of lung aging in senescence-accelerated mouse (SAM)**

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The SAM strains are a collection of inbred mouse strains developed as models of accelerated aging, and include nine short-lived, the senescence-prone strains (SAMP) and three longer lived control strains designated the senescence-resistant strains (SARD). The SAMP was suggested as a new murine model of aging lung. However, molecular mechanism of accelerated lung aging remains to be elucidated. By using quantitative real time RT-PCR and western blot, here we show that expression of FOXO, a forkhead transcription factor that acts downstream of the PTEN/P13K/Akt pathway and a key regulator of stress resistance, metabolism and aging, was significantly decreased in aged SAMP mice compared to normal aging control SARD mice. The decreased expression of FOXO gene was correlated with elevation of reactive oxidative species (ROS) and thiobarbituric acid reactive substances (TBARS), reduced mRNA expression levels of superoxide dismutase (SOD) and lung and renal caspase 3, 7 and 9 (casp 3, 7 and 9) as well as greater right ventricular hypertrophy and cardiac fibrosis in SAMP mice lungs. Based on these findings we concluded that reduced FOXO activity may contribute to accelerated lung aging in this animal model. Given that FOXO proteins play a critical role in maintaining the quiescence and renewal capacity in hematopoietic stem cells and neural stem cells, manipulation of FOXO in lung progenitor cells may represent a novel approach to lung regenerative medicine and chronic lung disease such as COPD.

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**Aging and smoking contribute to plasma surfactant proteins and protease imbalance with correlations to airway obstruction**

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**Background:** A significant number of young people start smoking at an age of 13-15, which means that serious smoking-evoked changes may have been occurred by their twenties. Surfactant proteins (SP) and matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) have been linked to cigarette smoke induced lung remodelling and COPD. However, the level of these proteins has not been examined during aging or in young individuals with short smoking histories.

**Methods:** Plasma levels of SP-A, SP-D, MMP-9, and TIMP-1 were measured by ELISA/ELISA from young (18-23 years) non-smoking controls (YNS) (n=56), smokers (YS) (n=51), middle aged/elderly (37-77 years) non-smoking controls (ONS) (n=40), smokers (OS) (n=64) (FEV1/FVC < 0.7 in all subjects) and patients with COPD (n=44, 35-79 years).

**Results:** Plasma levels of SP-A increased with age and in the older group in relation to smoking and COPD. Plasma SP-D and MMP-9 levels did not change with age but were elevated in OS and COPD as compared to ONS. The TIMP-1 level declined with age but increased in chronic smokers when compared to ONS. The clearest correlations could be detected between plasma SP-A vs age, pack years and FEV1/FVC. The receiver operating characteristic (ROC) curve analysis revealed SP-A to be the best marker for discrimination between patients with COPD and the controls (area under ROC curve of 0.842; 95% confidence interval, 0.785-0.899; p < 0.001).

**Conclusions:** Age has a significant contribution to potential markers related to smoking and COPD, SP-A seems to be the best factor in differentiating COPD from the controls.

P797

**Endothelial dysfunction in preterm infants with respiratory disorders**

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**Actualiy:** Respiratory disorders accompanied by endothelial disorders, but the clinical manifestations of changes in rates which characterize endothelial function in neonatology is neglected, because the purpose of our study was to establish clinical significance of endothelial dysfunction in preterm infants with respiratory disorders by the value of serum vascular endothelial growth factor (VEGF).

**Materials and methods:** The main group 67 children, who at birth had diagnosed respiratory distress syndrome. The average birth weight 1473,1±97,4 g, gestational age - 29±8.6 weeks. In the controling group were included 20 premature infants with birth weight 1529,5±82.8 g and gestational age 30,6±6,0 weeks without respiratory disorders.

**Results and discussion:** The values of serum VEGF at 5-7 day of life in children of all investigated groups did not differ significantly (by 124±93,1 and 135±83,2 pg/ml, p > 0.05). In dynamics, 28 day life, we set the negative trend in the core group of children (114,1±24,5 to 328,8±92,3 pg/ml in the comparison group, p < 0.05). Regression analysis established the relationship between the values of serum VEGF at 5-7 day of life and indicators of body weight (r=0,62, p < 0.05), duration of gestation at birth (r=0,64, p < 0.05) and indicators of body weight (r=0,62, p < 0.05) and duration of mechanical ventilation (r=0,89, p < 0.05).

**Conclusions:** The low value of VEGF for 5-7 day of life in preterm infants with respiratory failure and lack of growth in the dynamics indicate low ability to restore damaged capillaries and the risk of chronic disease.

P798

**Neutral sphingomyelinase 2 (nSMase2) has a protective role in emphysema**

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**Introduction & background:** nSMase2 is an enzyme converting sphingomyelin into ceramide. Others have expressed that nSMase2 activation and ceramide production are linked to emphysema development. The goal of this study was to test the effect of nSMase2 deficiency on lung phenotype in mice.

**Hypothesis:** The mouse mutant model for nSMase2 deficiency, nSMase2 -/-, is the most effective model of nSMase2 knockout due to the expression of nSMase2 encoding gene, rendering this enzyme inactive. In this study, we analyzed lung histology and lung function in adult nSMase2 -/- mice.

**Method:** Mean linear intercept (Lm) and alveolar destructive index (DI) were used to assess morphological changes in lungs. Lung compliance was measured to assess changes in lung function.

**Results:** We found that lungs of nSMase2-deficient mice exhibited emphysematous changes. Both Lm and DI were significantly increased in nSMase2 -/- mice.
study, for the first time, MV with and without recruitment manoeuvres (RM) was compared in healthy mice. The effects of RM on a variety of physiological parameters and pulmonary inflammation were studied after 6h.

C57Bl/6 mice were ventilated for 6h at low–VT=8mL/kg, f=180/min or high–VT=16mL/kg, f=90/min and 3% inspiratory CO2. FiO2 was 0.5 and PEEP 2cmH2O. RM were performed with 30cmH2O for 1s every 5min, 60min or not at all. Lung mechanics were followed by the forced oscillation technique. Blood pressure (BP), ECG, heart frequency (HF), oxygen saturation and body temperature were monitored. Blood gases, histopathology, neutrophil recruitment, microvascular permeability and pro-inflammatory cytokines were examined. MV with recurrent RM resulted in stable respiratory mechanics. Ventilation without RM worsened lung functions due to alveolar collapse, leading to impaired gas exchange. HF and BP were not affected. Microvascular permeability was highest in atelectatic lungs, whereas neutrophil recruitment and structural changes were strongest in lungs ventilated with high VT. Although IL-6 and KC were markedly elevated in all ventilated mice, levels were clearly reduced by recurrent RM. In contrast, TNF-α and IP-10 remained at baseline, indicating that only moderate lung injury was induced. We conclude that recurrent RM are required to prevent atelectasis and resulting lung injury during mechanical ventilation of healthy mice.

**P801**

Patterns of plasma membrane disruptions distribution in mechanically ventilated lungs

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**Rationale:** Abnormally high stresses applied to a cell can result in the loss of cell membrane integrity and the formation of direct communications between intracellular and extracellular spaces, called plasma membrane disruptions (PMD). These lesions could be involved in the genesis of biotaaurma as upregulators of pro-inflammatory mediators expression. Observations limited to the subpleural alveoli only indicate that PMD take place during mechanical ventilation with large tidal volumes (VT) and a normal end-expiratory lung volume (EELV). It is unknown if PMD develop during low EELV ventilation with physiological VT.

**Objectives:** To see if a) mechanical ventilation with physiological VT at low EELV causes PMD, and b) the parenchymal distribution of PMD differs between ventilation with large VT at normal EELV and ventilation with physiological VT at low EELV.

**Methods:** PMD have been detected as red spots in gelatin included slices of rat lungs stained with ethidium homodimer-1 shortly after anesthesia, after prolonged ventilation at low EELV followed or not by the restoration of physiological EELV, and after prolonged ventilation with large VT and normal EELV. Analysis of lavage fluid showed that both treatments abolished PMD differences between ventilation with large VT at normal EELV and ventilation with physiological VT at low EELV.

**Conclusions:** Entity and distribution of PMD depends on the type of injurious mechanical ventilation.

**P802**

Dexamethasone reduces lung inflammation induced by alveolar stretch in mice

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**Background:** Although mechanical ventilation is a life-saving procedure, the associated alveolar stretch can provoke lung injury (ventilator-induced lung injury, VILI). At present, it is thought that ventilator-induced lung injury may precede lung injury. Activated granulocytes are known to induce oxidative stress and protease activity in alveoli, causing alveolar-capillary barrier disruption and lung dysfunction.

**Aim:** To study the anti-inflammatory action of dexamethasone, a widely used glucocorticoid, in mice exposed to either low or high alveolar stretch.

**Methods:** C57Bl/6 mice were mechanically ventilated for 5 hours with either an inspiratory pressure of 10 cmH2O (“low” tidal volumes (VT) ∼7.5 mL/kg, LV=10 cmH2O) or 18 cmH2O (“high” VT ∼15 mL/kg, HV=18 cmH2O). Dexamethasone was intravenously administered at initiation of ventilation. Non-ventilated mice served as controls. Inflammatory mediator expression and granulocyte influx were determined in lung homogenates. Differential cell counts were done on BALI cytospin preparations.

**Results:** Both LV and HV ventilation increased inflammatory mediator ex-
pressure in lung tissue which was accompanied by granulocyte influx (p<0.05). BALf neutrophil numbers and inflammatory mediator expression (KC, IL-1) were enhanced in HV-ventilated mice compared to LV-ventilated mice (p<0.05). Dexamethasone inhibited lung inflammation caused by LV or HV-ventilation (p<0.05).

Conclusion: Dexamethasone prevents inflammatory mediator expression and granulocyte influx of lungs exposed to low or high alveolar stretch. Dexamethasone treatment may be considered as a potential therapeutic strategy to inhibit the inflammatory response during mechanical ventilation.

P803
Intermediolin stabilized endothelial barrier function and attenuated ventilator-induced lung injury in mice
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Rationale: Even protective ventilation may aggravate or induce lung failure, particularly in prejured lungs. Thus, new adjuvant pharmacologic strategies are needed to attenuate ventilator induced lung injury (VILI). Intermediolin/Adrenomedullin II (IMD) stabilized pulmonary endothelial barrier function in vitro. We hypothesized that IMD may attenuate VILI-associated lung permeability in vivo.

Methods: Human umbilical vein endothelial cell (HUVEC) monolayers were incubated with IMD and transendothelial electrical resistance was measured to quantify endothelial barrier function. Expression and localisation of endogenous pulmonary IMD and its receptor complexes composed of CRLR and RAMP-3 were analyzed by qPCR and immunofluorescence in unventilated mouse lungs and in lungs ventilated for 6h. In untreated and IMD treated mice, lung permeability and pulmonary leukocyte recruitment was assessed after mechanical ventilation.

Results: IMD stabilized endothelial barrier function in HUVECs. Mechanical ventilation reduced the expression of RAMP 3, but not of IMD, CRLR, and RAMP1 and 2. Mechanical ventilation induced lung permeability, which was ameliorated by IMD treatment. IMD did not reduce VILI associated pulmonary leukocyte recruitment.

Conclusion: We showed for the first time that IMD had endothelial barrier stabilizing properties in vivo. IMD may possibly provide a new approach to attenuate ventilator-induced lung injury.

P804
Plasma levels of LL37 in patients with and at risk of acute lung injury
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Cathelicidins are a group of antimicrobial peptides with a wide range of functions including immunomodulation, chemotraction, angiogenesis and antimicrobial effects. LL-37 is the active form of the only known human example of a cathelicidin, HCAP-18. It is induced by the local action of L-25-0H vitamin D. LL37 is expressed by many different cell types including lung epithelial cells, neutrophils and other immune cells. We have shown that patients with severe vitamin D deficiency have an increased risk of Acute Lung Injury post-oesophagectomy and hypothesized that this may be related to the effects of vitamin D on LL37.

Methods: Plasma levels of LL37 were determined by ELISA in a cohort of patients with Acute Lung Injury and in a cohort of patients at risk of Acute Lung Injury due to undergo oesophagectomy.

Results: Average pre-operative plasma LL37 levels in the oesophagectomy cohort were 117.2 ng/ml and post operative levels are significantly lower (p=0.027, paired t test). In our ALI cohort, median levels of LL37 on day 0 lower than normal levels (p=0.017). LL37 levels correlate with vitamin D status, however, preoperative LL37 levels did not predict Acute Lung Injury.

Conclusion: LL37 levels are lower than normal in patients with Acute Lung Injury and fall progressively in patients undergoing oesophagectomy. The mechanism underlying this is unclear and requires further evaluation, but may be related to vitamin D deficiency in these patients.

P805
Preventive and therapeutic effects of phosphoinositide 3-kinase inhibitors on acute lung injury
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Rationale: Acute lung injury and acute respiratory distress syndrome (ALIARDS) are severe disorders. Pulmonary injury is at the endothelial cell (EC) barrier with increased permeability. Our in vitro studies demonstrate that adenosine protects from the bacterial toxin lipopolysaccharide (LPS) induced barrier dysfunction.

Hypothesis: Based on the known activation of the A2A adenosine receptor (A2AR) with adenosine it was hypothesized that the A2A agonist, CGS 21680 (CGS), would attenuate the LPS disrupted EC barrier in vivo.

Methods: Control and A2AR knock out (KO) mice were given normal saline (NS) or LPS intratracheally. NS or CGS was instilled intravenously (IV) at the same time or 3hrs later. At 22 hours Evans Blue Dye albumin (EBD) was instilled IV, at 24hrs the samples were collected. Bronchoalveolar lavage (BAL) was done and the lungs harvested. Cell counts, protein and EBD extravasation were analyzed.

Results: LPS caused an increased number of cells in the LPS/adenosine treated mice and the KO mice treated with CGS at 3hrs consistently demonstrated a decreased cell count. LPS challenge increased the protein in BAL and EBD from lung, the protein and EBD were significantly attenuated in the LPS/adenosine treated mice but not in the CGS treated mice.

Conclusions: Adenosine significantly attenuates the LPS induced EC barrier dysfunction in mice. The A2AR agonist, CGS, attenuates the cell count but not the protein or EBD extravasation. Other adenosine receptors or mechanisms may be involved in the significant improvement of protein and EBD barrier disruption that occurs with adenosine treatment.
PN07
Use of lipids in a murine model of ALI and lymphocyte apoptosis – Harmful or beneficial?
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Acute lung injury (ALI) and sepsis remain major challenges in critical care. While a massive inflammation determines early sepsis, apoptosis of lymphocytes is a hallmark of late sepsis. Lipid emulsions (LE) base used in critically ill to maintain caloric intake. Fish oil (FO) based LE are considered as alternative with immunomodulatory impact. We investigated the effects of LE in a murine model of ALI.

Mice were infused with SO, FO or NaCl. 24 h after intratracheal instillation of 10 µg lipopolysaccharid (LPS), a bronchoalveolar lavage (BAL) was performed to determine numbers of leukocytes, protein and cytokines. Lymphocytes were isolated from spleen and apoptosis was determined by FACS. LPS induced a massive invasion of leukocytes into the airspace compared to unstimulated controls. Infusion of SO amplified whereas FO attenuated the rise. Both, insulin and FasL expression were increased which was further increased by SO. Infusion of FO reduced protein as well as TNF after LPS. Before LPS, infusion of SO induced a significant rise in apoptosis of lymphocytes. After LPS, a reduced number of lymphocytes accompanied with a rise in apopto-sis was detected in all groups with FO infused mice showing significantly less apoptosis compared to SO.

In a murine model of ALI the choice of lipid emulsions is able to influence inflammatory parameters. Induction of ALI is paralleled by reduced lymphocytes with increased apoptosis in the spleen. SO leads to massive apoptosis in lymphocytes even before ALI. Infusion of FO attenuated the rise in ALI-induced apoptosis. Modulating the lipid emulsions used for nutrition may be relevant for critically ill, and may have impact on outcome.

PN08
Eugenol dose-dependent improvement of pulmonary lesions in lipopolysaccharide acute lung injury
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Background: Eugenol, a methoxypyrenyl component of clove oil, inhibits NFκB activation induced by TNF-α in LPS-stimulated macrophages.

Aim: To evaluate the effects of different doses of eugenol on lung mechanics, histology and cytokines in LPS-injured lungs.

Methods: Mice were randomly divided into 9 groups (n=5-8/group). Mice received intratracheally sterile saline solution (0.05 ml) or LPS (10 µg in 0.05 ml of saline): 6 h later they received sterile saline (0.2 ml) and TNF-α (1% and 2% groups) or different doses of eugenol: 16, 65, 114, 160, 650 or 1140 mg/kg in saline (0.2 ml) and TNF-α (1% (LE1), LE2, LE3, LE4, LE5, LE6 and LE7 groups, respectively) by gavage. Mice were evaluated 24 h after receiving LPS. In another 18 mice [C=6, L=6, E=3 (saline followed by eugenol) and LE=3]; in theory similar; TNF-α or IL-10 were detected by ELISA in lung homogenates at 6 (C=3 and L=3) and 24 h (C=3, L=3, E=3 and LE=3) after LPS administration. One-way ANOVA followed by Tukey test was used (α=5%).

Results: Static elas-tance, viscoelastic component of elastance and viscoelastic resis-tive pressure were higher in L group (33.05, 5.01 cmH2O/ml and 1.00 cmH2O respectively) than in C (22.13, 3.62 cmH2O/ml and 0.71 cmH2O), accompanied by alveolar collapse and collagen fiber deposition; eugenol reduced the parameters compared to unstimulated controls. Infusion of SO amplified whereas FO attenuated the rise. Both, protein and TNF exhibited a LPS-induced rise which was further increased by SO. Unstimulated controls. Infusion of FO reduced protein as well as TNF after LPS. Before LPS, infusion of SO induced a significant rise in apoptosis of lymphocytes. After LPS, a reduced number of lymphocytes accompanied with a rise in apopto-sis was detected in all groups with FO infused mice showing significantly less apoptosis compared to SO.

Conclusion: Eugenol exhibits an in vivo anti-inflammatory dose-dependent action in LPS-induced lung injury. Supported by: CNPq, FAPERJ, MCT.

PN09
Increased uric acid levels in bronchoalveolar lavage fluid of mice infected with H1N1 influenza
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Rationale: Lower respiratory tract infections with influenza are associated with severe inflammatory responses, which may result in ALI/ARDS. Tissue injury results in the release of damage-associated molecular patterns (DAMPs), such as uric acid and ATP, leading to NLRP3 inflammasome activation and IL-1β release. Hypothesis: We hypothesized that influenza-induced lung injury is associated with the release of DAMPs into the airway lumen.

Methods: C57Bl/6 mice were inoculated with 10ICD50 influenza A/PuR8/34 (H1N1) and sacrificed 4, 8 and 14 days later to collect BALF to determine uric acid, extracellular ATP and markers of inflammation and lung injury. Non-infected mice were sacrificed on day 0 for control measurements.

Results: Influenza virus infection resulted in bodyweight loss between day 6 and day 11 (p<0.05) and returned to normal values on day 14 after infection. Uric acid levels in BALF were significantly increased on day 8 after viral infection (52.7-119.9 µM vs 12.2-25.8 µM in control mice, 95% CI: p<0.01), while ATP was undetectable. Uric acid in BALF was associated with increased levels of inflammatory markers (IL-6, KC and IFN-γ) as well as markers of lung injury (sRAGE and total protein in BALF). However, increased IL-1β levels, indicative for inflammasome activation, were only observed on day 4 after influenza infection (p<0.01).

Conclusion: Uric acid in BALF is increased during influenza infection and associates with biomarkers of inflammation and lung injury, but not with sRAGE. Our data suggests that Vitamin D plays a role in the maintenance of antigenic cell death. sFasL inhibited proliferation of ATII in actions that were protective against apoptotic cell death.

PN11
Modeling resolution of direct acute lung injury
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Translational animal models allowing the study of both inflammatory and resolution phases of acute lung injury (ALI) are lacking. Widely used models including intratracheal endotoxin or bleomycin are difficult to translate. Here we developed and optimized a reproducible model of resolving aspiration pneumonitis that mimics human ALI.

C57Bl/6 mice were instilled intratracheally with 75µl of 0.1M hydrochloric acid by direct laryngoscopy under anesthesia. At specified timepoints up to 10 days after instillation, respiratory mechanics, arterial blood gases, soluble mediators in bronchoalveolar lavage fluid (BALF), and alveolar fluid clearance (AFC) using an in situ preparation were measured. Acid instillation produced significant increases in BALF protein levels and respiratory elastance. BALF levels of TNF and soluble RAGE, a marker of epithelial damage, both increased, while AFC deteriorated. All of these parameters peaked at day 1-3 post-acid, but resolved by days 5-10. These results indicate that the model replicates major hallmarks of ALI, i.e. changes in respiratory mechanics, gas exchange, lung permeability, inflammation

Abstract PN01 – Table 1

<table>
<thead>
<tr>
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<th>Control (untreated)</th>
<th>3 hrs</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
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<tr>
<td>PaO2/FiO2</td>
<td>95±62</td>
<td>119±28**</td>
<td>162±71**</td>
<td>206±130**</td>
<td>262±156**</td>
<td>41±189</td>
<td>531±90</td>
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<td>BALF Protein</td>
<td>0.15±0.02</td>
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<td>4.86±0.47*</td>
<td>3.56±0.35*</td>
<td>1.72±0.89*</td>
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<td>ATP (µg/ml)</td>
<td>23±11</td>
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<td>338±20**</td>
<td>45±23</td>
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<td>AFC (%/30 mins)</td>
<td>10.95±0.97</td>
<td>8.11±0.24</td>
<td>7.19±2.3*</td>
<td>6.36±1.5**</td>
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One-Way ANOVA with Bonferroni test. Mean/SD. *P<0.01; **P<0.05 vs control. N=3–6/group per time point.
PL12
Fas activation impairs the alveolar epithelial function in mice by mechanisms involving apoptosis
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Background: Alveolar epithelial damage is a critical event that leads to protein-rich edema in acute lung injury (ALI). Even though Fas activation induces apoptosis of alveolar epithelial cells, its role in the formation of lung edema is unclear.

Aim: We investigated whether inhibition of caspase-dependent apoptosis protects against Fas-mediated alveolar epithelial injury in mouse lungs.

Methods: We administered the pan-caspase inhibitor Z-VAD.fmk (10 mg/kg) or vehicle subcutaneously to mice treated with one intratracheal dose of recombinant human fasL (rh-fasL; 50 ng) or PBS, then studied the mice 1 h later. We measured alveolar fluid clearance (AFC) by intratracheal instillation of FITC-human albumin, and protein permeability by measuring IgM in bronchoalveolar lavage fluid. Caspase-3 activity and cytokines (IL-β, IL-6, KC, TNF-α) were measured in lung homogenates.

Results: Compared with PBS-treated mice, the intratracheal instillation of rh-fasL decreased AFC (PBS: 20.1±1.5% vs rh-fasL: 19.6±1.4%, p<0.05), and increased protein permeability (PBS: 34.7±18.3 vs rh-fasL: 350±40.4 ng/mL, p<0.05), caspase-3 activity and cytokine production. In contrast, mice treated with rh-fasL and Z-VAD.fmk had normal AFC (17±0.3±3%, p<0.05) and a smaller increase in protein permeability (153±18.4 ng/mL, p<0.05), associated with a reduction in caspase-3 activity and an increase in cytokine production. Z-VAD.fmk was not harmful in PBS-treated mice.

Conclusion: Activation of the Fas pathway impairs the alveolar epithelial function in mouse lungs by mechanisms involving caspase-dependent apoptosis, suggesting that targeting apoptotic pathways could reduce the formation of lung edema in ALI.

PL13
Resolvin D1 attenuates lung inflammation in LPS induced-ALI partly through PPARα signaling
Zenglin Liao1, Jiajia Dong 1, Tao Wang2, Fuqiang Wen1.

± Reduction of caspase-3 activity and an increase in cytokine production. Z-VAD.fmk through PPARα signaling could reduce the formation of lung edema in ALI.

Introduction: Resolvin D1 attenuates lung inflammation in LPS induced-ALI partly through PPARα signaling.

Methods: Z-VAD.fmk decreased AFC (PBS: 20.0±18.3 vs rh-sFasL= 350±18.4 ng/mL, p<0.05, n=9). H&E staining of histological sections showed that RvD1 markedly reduced lung edema in ALI. In contrast, mice treated with rh-sFasL had increased protein permeability (PBS= 20.0±18.3 vs rh-sFasL= 1.9±0.5, n=9).

Results: Compared with PBS-treated mice, the intratracheal instillation of rh-sFasL decreased AFC (PBS: 20.0±18.3 vs rh-sFasL= 1.9±0.5, n=9), and increased protein permeability (PBS: 34.7±18.3 vs rh-sFasL: 350±40.4 ng/mL, p<0.05), caspase-3 activity and cytokine production.

Conclusion: Resolvin D1 attenuates lung inflammation in LPS induced-ALI partly through PPARα signaling. The lack of neutrophil infiltration did not affect lymphocyte migration to the airways, suggesting an independent mechanism drives this response.

PL15
Temporal characterization of murine genomic response to poly I:C stimulation reveals tri-phasic inflammatory response signatures
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Introduction: Poly I:C mimics a viral infection through the activation TLR3 and RNA helicases. Our aim was to characterize molecular changes occurring in the lung after poly I:C exposure in mice.

Methods: BALB/c mice were administered saline or poly I:C (30 µg/mouse) at 7 time points after dosing (2-168h), poly I:C and saline-treated mice were sacrificed, bronchoalveolar lavage was performed and lungs were snap-frozen. RNA from lung homogenates was isolated using the Norgen labeling method and assessed on a high density matrix standard murine whole genome array (MOE430 2.0 platform, Affymetrix). Differentially expressed genes were determined using an ANOVA, with pairwise comparisons between poly I:C and saline treatment at each timepoint. Functional pathways were determined using GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: The peak response occurred 6-48h post-treatment. Hierarchical clustering across the study revealed 3 distinct temporal clusters (early, mid, and late phase). Inflammatory processes were enriched in the early phase (2-4h), TLR/R-L1 signaling genes in the mid phase (6-48h), and cell cycle pathways in the late phase (>72h). GSEA revealed activated NK and dendritic cell signatures up to 96h post-challenge, while several immune and myeloid related gene modules were also up-regulated between 6-96h post-challenge.

Conclusions: Inflammatory signatures including TLR and IL-1-related genes were highly up-regulated in response to poly I:C challenge, indicating a strong inflammatory response potentially driven by NK and dendritic cells in the lungs of mice.

PL16
Molecular mechanisms are involved in ethanol mediated lung endothelial barrier dysfunction
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Recent studies have uncovered a significant but previously unknown correlation between alcohol (ethanol) abuse and the risk of acute respiratory distress syndrome (ARDS) [1]. Despite studies aimed at improving outcomes in patients with ARDS, the mortality remains high at > 40%. For those who abuse alcohol, the mortality is even higher, at 65% [2]. and therefore, alcohol abuse causes tens of thousands of excess deaths annually. One of the important functions of lung endothelium is to provide a barrier against the penetration of bacterial toxins in the circulation and endothelial junctional proteins act as a structural barrier against the paracellular permeation [3]. We hypothesized that excessive alcohol could negatively regulate the integrity of lung endothelial barrier and increases the risk during bacterial infections. Our novel preliminary data using human lung microvascular endothelial cells (HLMVEC) demonstrate that ethanol dose-dependently disrupts the EC barrier properties as evidenced by Electric Cells-Substrate Impedance Sensing (ECIS) based transendothelial electrical resistance measurement. Pretreatment of the HLMVEC with LPS and subsequent challenge with ethanol disrupts the tight junctional proteins and increased phosphorylation of myelin light chain across the study revealed 3 distinct temporal clusters (early, mid, and late phase). Inflammatory processes were enriched in the early phase (2-4h), TLR/R-L1 signaling genes in the mid phase (6-48h), and cell cycle pathways in the late phase (>72h). GSEA revealed activated NK and dendritic cell signatures up to 96h post-challenge, while several immune and myeloid related gene modules were also up-regulated between 6-96h post-challenge.

Conclusions: Inflammatory signatures including TLR and IL-1-related genes were highly up-regulated in response to poly I:C challenge, indicating a strong inflammatory response potentially driven by NK and dendritic cells in the lungs of mice.

References:
P817 Effect of proteinase inhibitor from crataeva tapia (cratatal) in distal lung mechanical, inflammatory and remodeling alterations induced by elastase in mice
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Aims: The leading role of elastase in the emphysema pathophysiology has been recognized. The present study aimed to evaluate if a plant proteinase inhibitor Cratatal contributes to inactivation of elastase-induced mechanical, inflammatory and extracellular matrix remodeling alterations.

Methods: C57Bl/6 mice received elastase intranasally (50µL/animal E group). Control group received saline (W group). Afterwards, mice were treated with Cratatal (2mg/kg) at days 1, 5, 21, 28, 35 after elastase instillation (1-E group). At day 40, mice were anesthetized and mechanically ventilated and we analyzed respiratory system resistance and elastance, tissue elastance, tissue damping and airway resistance. Afterwards, BAL was performed and lungs were removed. By morphometry, we quantified the mean linear intercept (Lm) and the collagen and elastic fibers in distal lung parenchyma.

Results: We did not observe any differences in pulmonary mechanics comparing all groups. In E group, there was an increase in BAL-total cells, BAL-lymphocytes, BAL-neutrophils, collagen and elastic fibers and Lm compared to E group (p<0.05). The Cratatal treatment in elastase treated animals decreased Lm (105.9±10.6µm) compared to E group (p<0.05) BAL-lymphocytes (7.2±1.4×10³ cells/µL), and collagen content (0.59±0.02%) were decreased in 1-E group compared to E group (p<0.05).

Conclusions: This plant proteinase inhibitor (Cratatal) reduced elastase-induced pulmonary inflammatory and remodeling alterations which may be considered as a new and potential therapeutic strategy for COPD treatment.

Financial support: FAPESP, CNPq, LIM-HCFMUSP.

P818 Intravenous immunoglobulin in community acquired pneumonia
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Immunity disorders play an important role in the inflammatory formation in patients with lung diseases.

The aim was to study the efficacy of i.v. immunoglobulin immunovin (IMV) in patients with community acquired pneumonia (CAP).

Methods: The study included 35 patients with CAP. The patients blood was tested to estimate the level of CD3+, CD4+, CD8+, CD16+, CD20+ lymphocytes, the content of A.G.M immunoglobulins (IGM), circulating immunocomplexes (CIC), γ-interferon and TNFa. 17 patients with CAP were treated with standard therapy. The other 18 patients received combined treatment with IMV.

Results: Compared to healthy subjects in patients with CAP the level of CD3+, CD4+, CD8+, CD16+ and CD20+ lymphocytes was lower by 1.2-1.4 times, the content of IgA, IgG and γ-interferon was lower by 1.3 times. Conversely, the level of CD20+ lymphocytes, IgM, CIC was higher by 1.3-1.8 times, and the level of TNFa was higher by 1.5 times. Symptoms of inflammation and impairment of the immune status have been found in patients who received standard therapy. The use of IMV in patients with CAP eliminated immunity disorders, improved the results of the treatment.

Conclusion: In patients with CAP immunovin improved the immunity status and increased the treatment efficacy.

P819 PTX3 as a component of innate immunity in the role of captoril in acute lung injury induced by bacterial endotoxin
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Objective: Innate immunity is an important mechanism for the development of acute lung injury (ALI). Lung pentraxin PTX3 is an inflammatory mediator and a component of innate immunity. Recent evidence indicates that angiotensin-converting enzyme (ACE) plays an important role in the pathogenesis of ALI. We speculated that inhibition of ACE play the protective effect on ALI through the prevention of PTX3, S.O2, protect the lung from injury.

Methods: Lung injury was induced by intratracheal instillation of lipopolysaccharide (LPS) in rats, followed by i.p. administration of captoril, an ACE inhibitor, or saline control, and the PTX3 expression, fibrin deposition, tissue factor expression and lung injury were determined. Local and systemic inflammatory responses were assessed by measuring cytokines in the lung and plasma.

Results: Treatment with captoril dramatically attenuated LPS-induced lung injury, alleviated fibrin deposition and inflammatory cell infiltration 6 hours after LPS challenge compared to that in the saline control rats. Local and systemic PTX3 expression were significantly decreased by the captoril therapy, accompanied by decreased interleukin (IL)-6, IL-10 and monocyte chemoattractant protein-1 levels in the plasma.

Conclusion: These results support that inhibition of ACE with its clinically used inhibitor offers protective effects on ALI; PTX3, acting as both anti-inflammation component and the component of innate immunity, may reflect severity of lung injury and serve as the predictor of therapeutic effect. The PTX3 treatment through the presence of PTX3 could be a potential mechanism that mediates lung injury.

P820 Effect of ketonazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in healthy subjects
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Rationale: A combination of the novel corticosteroid FF and long acting beta2-agonist VI administered via dry powder inhaler (FF/VI) is being developed as one of a new therapeutic strategy for COPD. Both FF and VI are predominantly metabolised via CYP3A4 and their PK and PD could be affected by CYP3A4 inhibition.

Objective: To investigate the effects of the strong CYP3A4 inhibitor ketonazole on the PK and PD of FF and VI.

Methods: Double-blind, randomised, placebo (P)-controlled, repeat dose, two-way crossover study. Healthy male and female subjects (N=18) received once daily oral ketonazole (400mg) or P for 11 days with FF/VI (200/25mcg) for the final 7 days. PD and PK data were obtained up to 48h following the Day 11 dose.

Results: Co-administration of ketonazole and FF/VI had no effect on 0-4h maximum heart rate or minimum blood potassium (treatment difference [90%CI] -0.60pm [-5.8, 4.5] and 0.04mmol/L [-0.03, 0.11], respectively) whilst there was a measurable but clinically insignificant decrease in 24h weighted mean serum cotidol (treatment ratio [90%CI] 0.73 [0.62, 0.86]). Co-administration of ketonazole increased (percent change [90%CI]) FF AUC(0-24) and Cmax by 36% [19, 56] and 33% [12, 58] and VI AUC(0 t') and Cmax by 65% [38, 97] and 22% [-8, 38], respectively. Both treatments were well tolerated and there were no serious adverse events or withdrawals.

Conclusion: Co-administration of FF/VI with ketonazole resulted in less than two-fold increase in systemic exposure to FF and VI with no clinically significant systemic effect.

Funded by GSK (HZA105548; NCT01165125)

P821 Vilanterol, a novel inhaled long-acting β2-adrenoceptor agonist (LABA), demonstrates extensive first pass clearance to metabolites with negligible pharmacological activity in man
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Introduction: Vilanterol (VI) trinitrate is a novel LABA with demonstrated 24-hour clinical duration of action, currently in development in combination with an inhaled corticosteroid for once-daily treatment of COPD & asthma.

Objectives: The excretion and metabolism of radio-labelled VI was investigated following oral dosing to represent the swallowed portion of an inhaled dose. Co-administration of ketoconazole and FF/VI had no effect on 0-4h maximum heart rate or minimum blood potassium (treatment difference [90%CI]

Methods: Open label, single dose study. Healthy male subjects [N=6] received an oral solution dose of 200 µg of [14C]VI (2 µCi). Plasma samples and all urine and faeces were collected up to 168 h post dose and analysed for total radioactivity, VI and VI metabolites as appropriate.

Results: VI was well absorbed (>50% of the radioactive dose). VI represented a very small percentage (<0.5%) of the total circulating drug-related material in the plasma indicating extensive first-pass metabolism of VI. In total 70% of the recovered radio label was collected in the urine with the remainder recovered in the faeces. The primary route of clearance of VI was via O-dealkylation to metabolites with negligible pharmacological activity in man

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Conclusion: VI undergoes extensive first-pass metabolism in man. VI was well tolerated after an oral dose (200 μg) considerably in excess of the likely clinical inhaled dose (25 μg), indicating absent pharmacological activity of the metabolites in man (in agreement with pre-clinical data).

Funded by GSK (B2C106181; NCT01286381)

P824 The safety, tolerability, pharmacodynamics and pharmacokinetics of inhaled fluticasone furoate (FF) and vilanterol (VI) are unaffected by administration of codeine

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Introduction: A combination of the novel corticosteroid FF and long acting beta2-agonist VI (FF/VI) is currently under development as a once-daily inhaled treatment for asthma and COPD.

Objectives: To assess whether the pharmacodynamics (PD) and pharmacokinetics (PK) of FF and VI are affected when delivered as the FF/VI combination in combination with FF and VI alone administered from the same novel dry powder inhaler.

Methods: Single centre, randomised, double-blind, placebo-controlled, four-way crossover study. Healthy male and female subjects [N=16; 21-57 years] received single, supra-therapeutic doses of FF (800μgmcg), VI (100mcg), FF/VI (800/100mcg) and placebo. PK and PD were monitored post-dose.

Results: FF/VI decreased serum cortisol (0.24g weighted mean vs placebo) by 14.7% vs 24.1% for FF alone; the difference of 12.3% (90% CI: 4.4, 20.9) was considered non inferior (defined as lower CI > -20%). FF/VI increased heart rate (0.05 vs 0.15 max vs placebo) by 0.72pm vs 6.99pm for VI alone; the difference of 1.26pm (90% CI: 4.6, 2.1) was considered non inferior (defined as upper CI < +10.9pm). There were no differences in minimum blood potassium (0-4h). FF and VI mean exposure (AUC0′-∞/Clast∞) for VI were 15% (5, 24) and 3% (4, 14) lower, respectively, for the combination vs FP or VI alone. The adverse event profile for all treatments was similar to placebo.

Conclusion: Administration of FF and VI in combination was not associated with an increase in systemic exposure or systemic pharmacodynamic effects compared with administration of either compound alone.

Funded by GSK (HZA105871; NCT00588057)

P825 Aspirin inhalation treatment for COPD patients: Preliminary studies on PK and inflammatory biomarkers

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We are currently investigating if the use of aspirin (ASA), administered via inhalation, can exert a local anti-inflammatory effect, to propose it as a treatment for COPD, an inflammation-related pathology.

As little is known on inhaled ASA’s PK, a 3-way crossover study was performed on 14 moderate COPD subjects, which were administered 250/500/750mg of ASA’s b.i.d (aspirin tablets) 14 days. As little is known on inhaled ASA’s PK, a 3-way crossover study was performed on 14 moderate COPD subjects, which were administered 250/500/750mg of ASA’s b.i.d (aspirin tablets) 14 days.

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As little is known on inhaled ASA’s PK, a 3-way crossover study was performed on 14 moderate COPD subjects, which were administered 250/500/750mg of ASA’s b.i.d (aspirin tablets) 14 days.
Objective: To investigate pharmacokinetic of B17MP (active BDP metabolite) and Formoterol in children with asthma after inhalation of CHF 1535 50/6 μg via the licensed free combination of BDP and Formoterol dispersed with AeroChamber Plus™.

Methods: 22 children (5-11yrs) with mild asthma were included in this open-label, randomised, 2-way cross-over study of inhaled BDP 200μg and Formoterol 24μg. Eight-hour pharmacokinetic profiles (Cmax and AUROC) for B17MP and Formoterol after single inhalation were primary endpoints evaluated by analysis of variance and 90% bioequivalence limits.

Secondary endpoints were pharmacodynamics: serum potassium, heart rate, and cortisol excretion.

Results: B17MP and Formoterol pharmacokinetic parameters showed comparable values and the upper limit of the 90% CI was well within the bioequivalence limit. The pharmacodynamic parameters also showed similar values after both treatments.

Conclusion: After CHF 1535 506μg administration, the BDP and Formoterol systemic exposure was similar to the systemic exposure of BDP and Formoterol administered as free combination supporting a comparable safety profile in children aged 5-11yrs.

P827

Contamination and carry-over in clinical pharmacokinetic trials with aerosolized budesonide

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Background: Contamination and carry-over by active drug components is a major issue, especially in pharmacokinetic studies carried out with aerosolized substances. Measures to avoid contamination and carry-over in blood samples remain poorly standardized and validated.

Objective: To investigate the space- and time-related distribution pattern of budesonide aerosolized via MDI.

Methods: A matrix of crystallization dishes was set up in a measurement chamber. One puff of budesonide MDI (184 μg emitted dose, 200 μg nominal dose) was aerosolized and aerosol was allowed to sediment for 0.25 to 6.5 hours. Recovery of budesonide in the crystallization dishes was measured via HPLC and correlated to time course and spatial matrix.

Results: In 1 m distance of actuating the MDI, a mean recovery of budesonide of 0.688 μg after 0.25 hours and 1.423 μg after 6.5 hours was observed. The surface concentration in 1 m distance was 9.7 ng/cm² after 0.25 hours and 20.1 ng/cm² after 6.5 hours.

Conclusion: This study is a valid basis for risk assessment of carry-over effects in clinical trials with aerosolized drugs. Regarding surface concentrations in the nanogram range as shown in our study compared to serum drug concentrations in the picogram range, the carry-over effects via aerosols seem probable. Further studies to determine the extent and origin of these effects will therefore be performed.

P828

Fluticasone/salmeterol combined in the new Forspiro® inhaler is as effective and safe as Seretide® Accuhaler® in adult and pediatric asthmatics

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Objective: To compare the clinical efficacy and safety of fluticasone/salmeterol (FluSalm) combined in the new “Forspiro” DPI with Seretide Accuhaler (Glaxo Wellcome).

Methods: We conducted two large clinical phase III studies with twice daily treatment over 12 weeks including more than 770 children and adolescents/adults suffering from moderate or moderate-to-severe asthma. Primary endpoints were FEV1 change from baseline and the area under the FEV1 curve at study termination. Asthma symptom score, reliever use, morning PEF, adverse events (AEs) were also assessed.

Results: Mean increase of FEV1 for the 100/50 mcg (low dose) was 276 mL in adolescents/adults and 476 mL in children aged 6-11 years, and 344 mL for 500/50 mcg (high dose) in adults at endpoint. Morning PEF increased with the low dose by 17.5 L/mm in adolescents/adults and 31.5 L/mm in children, and by 35 L/mm with the high dose in adults. Asthma symptom scores and reliever use had already decreased substantially after the first treatment week. The number of drug-related AEs was comparable between treatments. Serum cortisol measured after 12 hours at endpoint tended to lower levels with the reference product. Patients’ assessment at study termination revealed an overall preference for the “Forspiro” DPI due to its mouthpiece fit, device size and shape.

Conclusions: FluSalm in the “Forspiro” inhaler was shown to be as efficacious and safe as Seretide Accuhaler.

P829

Effect of systemic and extra-fine particle inhaled corticosteroids on corrected alveolar nitric oxide (CANO) in COPD

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Background and objectives: Alveolar nitric oxide or (CANO), has been used as a surrogate marker of distal airway inflammation, which is important in COPD. Coarse particle inhaled corticosteroids (ICS) do not suppress CANO. We evaluated whether extra-fine particle size ICS or systemic oral corticosteroids could suppress CANO in COPD.

Methods: COPD patients with a smoking pack history >15 years, FEV1/FVC ratio <0.7, FEV1<80% predicted with small airways inflammation characterized by CANO >2ppb underwent a double-blind randomised controlled crossover trial with an open label systemic steroid comparator. Following a 2wk steroid washout period, patients were randomised to 2wks, 100mcgHFA-BDP-1 puff bid and then 2 weeks 400mcgHFA-BDP or matched placebos with subsequent crossover. All patients received 1wk open-label, 25mg/day prednisolone. Spirometry, body plethysmography, impulse oscillometry and exhaled nitric oxide were recorded.

Results: 16 patients completed per protocol. Compared to respective placebo there were no significant differences with extra-fine particle ICS. Oral prednisolone caused a significant reduction in FENO and JawNO but not CANO (see table1).

Conclusions: Whilst CANO remains a biomarker of interest in COPD, it is not suppressed by systemic or extra-fine particle ICS. Hence CANO is unlikely to be a useful marker for monitoring response of small airway disease to therapies in COPD.

P830

Lung deposition of the extra fine dry powder fixed combination beclomethasone dipropionate plus formoterol fumarate via the NEXT DPI® in healthy subjects, asthmatic and COPD patients

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Background: Chiesi has developed the new pocket size, medium air flow resistant, breath actuated multidose-reservoir dry powder inhaler NEXT DPI®.

Objectives: The lung deposition and distribution pattern of the extrafine fixed combination of beclomethasone dipropionate 100μg and formoterol fumarate 4μg administered via the NEXT DPI® was assessed using a gamma-sciagraphic technique after inhalation of a single dose of the 137mCs-radio labelled combination (total dose BDP/formoterol 400/24μg).

Methods: 10 healthy subjects, 9 asthmatic patients (30%≤FEV1<80%) and 9 patients with stable chronic obstructive pulmonary disease (COPD) (FEV1/FVC<70%, 30%<FEV1≤50%) were treated according to an open, single dose design.

Results: Similar lung and extra-thoracic deposition were observed between the groups. The average lung deposition was 55% relative to the emitted dose in healthy subjects, 56% in patients with asthma and 55% in COPD patients. The extra-thoracic deposition was 43% in healthy subjects, 42% in asthmatic patients and 42% in COPD patients. The amount exhaled ranged between 1.6 to 3.3%. The distribution pattern, evaluated by measuring the central/peripheral (C/P) ratio confirmed distribution throughout the airways, including periphery (C/P 1.23, 2.02 and 1.57 for healthy subjects, asthmatic and COPD patients, respectively).

Conclusions: These results demonstrated that a high amount of the extrafine dry powder fixed combination BDP/formoterol administered via the NEXT DPI® was deposited in the lungs regardless of the pathological condition.

Research funding source: Chiesi Farmaceutici S.p.A.
A novel NEXT DPI® dry powder inhaler and its use in asthmatic and COPD population
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Rationale: In asthma and COPD the dry powder inhalers (DPJs) facilitate patient’s compliance to drug intake. Chiesi Farmaceutici developed a new inhaler, NEXT DPI® which is pocket size medium-resistant breath-actuated mechanism (BAM) multidose-reservoir to be used for drug delivery.

Objective: To verify that the peak inspiratory flow (PIF) required for the drug delivery is not influenced by patient’s age and disease.

Methods: Children (n=27; age 5-11), adolescents (n=20; age 12-17) and adults (n=21; age ≥ 18) with asthma and COPD patients (n=21; age ≥ 40) were included in this multicenter open-label placebo study. After baseline pulmonary function assessments (FEV₁, FVC; PIF tested with spirometer and In-Check Dual® device) patients inhaled through the NEXT DPI® to test the BAM activation, checked by the BAM counter and made to take the right number of inhalations. Usability evaluation questionnaire, adverse events (AE) and vital signs were also recorded.

Results: In all patients, spirometry showed from moderate to severe airways obstruction. All patients, irrespective of age and disease, were able to activate the BAM. The mean PIF value (asthmatic patients: 104.4±20.6 L/min, range 40-120; COPD patients: 97.9±18.8 L/min, range 51-120) measured with the In-Check was greater than the threshold set for the BAM activation and not influenced by age and disease severity. No patients had problem in using the NEXT DPI® correctly. A total of 7 AEs were reported in 5 patients, no one related with the use of NEXT DPI® or severe in intensity. No Severe Adverse Events were reported.

Conclusions: NEXT DPI® can be easily used and activated in a wide population of asthmatics and COPD patients irrespective of age and disease severity.

P832 Efficiency of ipratropium bromide and salbutamol deposition in the lung delivered via a soft-spray inhaler or chlorofluorocarbon metered-dose inhaler
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Purpose: The dose combination of ipratropium bromide (Ib) and salbutamol (Sb) presently marketed in a single canister dosage form. A soft-spray, aqueous solution-based delivery system of this combination was developed. This pharmaco-kinetic study compared the efficiency of a soft-spray delivery of the combination to the lung compared to CFC delivery.

Methods: Inhalation of a 1:1 Ib:Sb solution was tested in a four-center substudy comprised of 278 patients conducted from two trials differing only by doses evaluating Ib and Aib delivered via the soft-spray inhaler or CFC-MDI in 2,578 patients. Ib alone delivered via the soft-spray inhaler and placebo delivered via either delivery system were used as controls. LCMS/MS assays for analytes were developed for plasma and urine biofluids.

Results: Comparing AUC, Cmax, and Cmin showed that systemic exposure to Ib and Sb delivered via the soft-spray inhaler was proportional to the doses delivered. Comparability was obtained when comparing the soft-spray inhaler-delivered Ib at half the dose of the CFC-MDI. Since Ip is not significantly absorbed from the gastrointestinal tract, the systemic exposure observed is a relevant marker for lung deposition. Ib alone gave equivalent exposure as the combination demonstrating a lack of interaction.

Conclusions: These systemic exposure analyses can be regarded as a marker of lung deposition and therefore demonstrate that the soft-spray inhaler delivers drug more efficiently to the lung than CFC-MDI.

P833 Maintenance of lung function and asthma control with extrafine beclomethasone/formoterol
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Introduction: Asthma management focuses on achieving and maintaining asthma control. Very few studies have assessed whether complete and sustained asthma control is maintained after switching ECSLABA fixed combinations in clinical practice.

Aim: To demonstrate equivalence between equipotent doses of extrafine BDPF pMDI and Budesonide/salmeterol (FP/S) (Diskus®) in maintaining lung function and asthma control.

Methods: Prospective, double-blind, double-dummy, randomized, parallel group, controlled trial. 416 asthma patients controlled on FP/S 500/100 μg/day (Disku®, pMDI or separate inhalers) were randomized to 12-week treatment with extrafine BDPF/FP/S 500/100 μg/day (Diskus®). Pre-dose FEV₁ was the primary outcome, secondary outcomes included asthma control (ACQ-7).

Results: At the study end, pre-dose FEV₁ was equivalent between treatments (difference between means 0.01 L; 95% CI -0.03 to 0.06 L) with no changes from baseline in both groups. ACQ-7 score was equivalent between groups (Table 1). Post-dose FEV₁ in the first hour was significantly higher for extrafine BDPF/FP/S pMDI both at baseline and after 12-week treatment (Fig. 1, Table 1). No safety issues were reported in both groups.

Conclusions: Patients previously controlled with FP/S in any device formulation can safely switch to extrafine BDPF/FP/S pMDI and maintain an equivalent asthma control with a sustained faster onset of action.

P834 Phase II study of once-daily GSK573719 inhalation powder, a new long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD)
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Introduction: GSK573719 is a new long-acting muscarinic antagonist offering sustained 24-hour bronchodilation in development for the treatment of COPD.

Objectives: To evaluate the safety, tolerability and pharmacokinetics of inhaled GSK573719 in a new dry powder (DP) formulation in COPD patients.

Methods: In this randomised, double-blind study, 38 patients with COPD received GSK573719 (250 μg.n=20; 1000 μg.n=9) or placebo (n=9) via a novel DP inhaler (DPI) once daily for 7 days.

Results: Of 43 adverse events (AEs) in 21 (55%) patients, 16 were drug related (all mild or moderate): placebo, 4 (headache, pruritus, flushing, hypoaesthesia); GSK573719 250 μg, 5 (arthrythmia, tachycardia, dyspnoea, hypertension, bronchospasm); GSK573719 1000 μg, 7 (blood pressure increase, thirst, oropharyngeal pain, headache, dry mouth, dyspnoea, feeling abnormal). Of 3 AEs related with withdrawals (chest pain, respiratory tract infection, dyspnoea), only dyspnoea was considered drug-related (1000 μg). The 1000 μg dose showed larger increases than 250 μg in heart rate (HR) (0–4h) vs placebo, but 24-h Holter monitoring showed no dose effect over 24h and the treatment effects were small. GSK573719 was rapidly absorbed (tmax 5–15min); 1–2% of the total dose was excreted unchanged in the urine. Accumulation (Day 7:Day 1) was low: 1.5–1.9x based on plasma data (1.8–2.4x, urine data). No correlation was seen between individual maximum HR increase and drug exposure.

Conclusions: GSK573719 250 μg or 1000 μg once daily by novel DPI was well tolerated by patients with COPD.

Funded by GlaxoSmithKline (CA4105211; NCT00732472)

140s
P835
Optimization of inhalation treatment – Evaluation of influence of PNEUMOlogic® and Optimiser® spacers on aerosol particle distribution from pMDI-EB
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Introduction: PNEUMOlogic® ([PNL]; the first inhalation chamber [vol. 800 ml] integrated with the spironeter, used for the controlled drug delivery from pMDI-EB. Optimiser® ([OPT]; [vol. 50 ml] is the aerosol chamber used for drug administration from pMDI-EB. The aim of the study was to evaluate the influence of inhalation chamber and method of performing inhalation on the quality of aerosol.

Method: Aerosol particle distribution and mass of aerosol was measured using particle counter with constant flow of 28,3L/min. Aerosol particle distribution and mass of aerosol was measured using Copley Inhalation Testing Data Analysis Software (CITDAS). The study was performed on the quality of aerosol.

Aerosol device was characterized by a cyclostyled effect on the inlet gas which reduces the oxygen velocity at the outlet.

Results: Intra nasal humidity dropped significantly from 40.3±8.7% to 29.0±6.8% at a flow rate of three litres when oxygen was given intranasally without humidification (p<0.01). We observed no significant change in airway humidity when oxygen was given prenasally and without humidification.

Conclusion: We propose two mechanisms to be responsible for this phenomenon: First prenasal application with low outlet velocity of dry oxygen allows for absorption of humidity from the surrounding air prior to nasal entry and second intranasal application with a high exit velocity from the applicator system might dry out the nasal mucosa by means of convection. Nasal oxygen application with the Optimiser device might obviate the need for humidification and therefore might simplify application and reduce therapy cost.

P836
In vitro comparison of aerosol characteristics of HFA ipratropium bromide pressurized metered dose inhaler (pMDI) formulation from threevalved holding chambers (VHCs)
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Inhaled bronchodilators and anticholinergics are the mainstay in the management of patients with chronic obstructive pulmonary disease. This study compared the in vitro aerosol characteristics from an HFA-steroid formulation pMDI (Atovent, 20 μg ipratropium bromide, Boehringer Ingelheim Ltd) with two anti-static VHCs, a preproduction OptiChamber Chamber (Diamond; Philips Respironics) and an Aero Chamber Plus Z-Stat (Z-Stat; Monaghan Medical Corp.) VHC, a conventional AeroChamber Plus (AC+; Monaghan Medical Corp.) VHC, and the pMDI alone.

Six pMDIs were primed before use and six of each VHC were washed and air dried. For each run (n) the pMDI was actuated into the VHC or next generation impactor (NGI) (for pMDI alone - tested before and after VHC tests), followed by 20 x's repetition at 30 L/min, repeated 10 times. Drug deposits from the NGI were analyzed using HPLC. The Emitted Dose (ED; drug entering the NGI), Fine Particle Fraction (FPF%; of ED in particles ≤ 4.7 μm), and Mass Median Aerodynamic Diameter (MMAD) were determined using Copley Inhalation Testing Data Analysis Software (CITDAS).

Table 1. Results: Mean (SD) [range]

Using a PIFR <90L/min for slow flow with a TID of 0.9–2 seconds for good co-ordination only for CHILD; 4 ADULT and 6 COPD demonstrated a good inhalation technique. The PIFR of 15 CHILD was <90/min, 26 ADULT and 24 COPD. 9 CHILD actuated too early, too late and 2 did not actuate. 17 ADULTS actuated too early, 27 were too late and 5 did not actuate. 9 COPD actuated too early and 14 too late. The mean (SD) ADULT ACQ of 2 was 0.14 (0.10) with no difference between slow and fast PIFR and co-ordination. ACQ for those with a good (n=4) and poor technique (n=56) was 1.07 (0.36) and 2.08 (1.02). As expected MDI co-ordination (TID) was poor and most PIFRs were too fast. The low IV and short Ti reveal that patients need to exhale more and prolong their inhalation time.

P839
In vitro nebulised dose emission characteristics of a tobramycin solution (75mg/ml) using an I-NEB (I-NEB) and a pari LC+ driven by a turbodrive compressor (PARI) nebuliser
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In practice solutions are nebulised by the equipment that is available rather than that recommended in the Summary of Product Characteristics (SPC). We have compared the in vitro aerosodynamic droplet characteristics of Brantium when used as a nebuliser by PARI (Pari GmbH), recommended in the SPC, and an I-NEB (Philips Respironics, UK) with a 300µl cup. We have previously adapted the com- positional methodology for nebulisers (Adelrahim & Chrystyn, J Aerosol Med 2009) and modified this to incorporate breath simulation (BS, tidal volume of 500ml and an inspiration: expiration ratio of 1:3) for use with I-NEB. The schematic design of our methodology is shown in figure 1.

The mean (SD) aerosodynamic droplet characteristics of tobramycin nebulised using PARI until spurring and I-NEB until dryness are summarised in Table 1. From the I-NEB data the fine particle dose (FPD) is 8.3mg. Separate determina- tions using PARI and compositional methodology provided a FPD of 17.5mg. The in vitro droplet emission characteristics suggest that 2 separate doses of Brantium
nebulised using an I-Neb with a 300ml cup could be comparable to 4ml nebulised by a Pari LC+.

95. Translational models of disease

P842 Non-genomic effect of glucocorticoids on inhibition of expression of CD63 on peripheral blood basophils

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Background: Glucocorticoids (GC) could inhibit histamine release from rat peripheral mast cells within 10 minutes, which classical genomic mechanism could not explain. The clinical efficacy of inhaled corticosteroids combined with long-acting beta 2-agonists has been widely demonstrated in asthma.

Objective: In order to validate the benefit of the combined these agents in vitro, we studied a rapid effect of fluticasone propionate (FP) and formoterol (FORM) alone and in combination on inhibition of expression of CD63, which is a marker of degranulation of basophils, in house dust mite (HDM)-sensitive patients with asthma.

Methods: Whole peripheral bloods from asthmatic patients were incubated with HDM for 20 min in the pretreatment of FP and/or FORM for 1 hour. We assessed the expression of CD63 on basophils by quantifying the mean fluorescence of CD63 in IgE-positive cells by FACS analysis.

Results: A high concentration of FP (10-8 M) alone, but not a low concentration of PP (10-12 M) alone, inhibits CD63 expression induced with HDM. The combination of FP (10-8 M) and FORM (10-7 M) more inhibits CD 63 expression on basophils.

Conclusion: The study provided evidence that non-genomic mechanism might be involved in rapid effect of glucocorticoids on basophils in asthma.

P843 Expression and functionality of P-glycoprotein in human bronchial epithelial cells in vitro

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P-glycoprotein (P-gp) is expressed in normal tissues with barrier functions where it participates in cell defence mechanisms (Huls, M. et al. J Pharm Exp Ther 2009; 328:3-9). Its presence in the bronchial epithelium and role in lung protection is still uncertain.

The human bronchial epithelium cell line Calu-3 and normal human bronchial epithelial (NBHE) cells were cultured at an air-liquid interface on Transwell® inserts for 21 days. P-gp expression was evaluated by quantitative polymerase chain reaction and its functionality was assessed by permeability measurements using the established substrate 3H-digoxin either alone or in the presence of chemical or molecular inhibitors.

P-gp was absent in NBHE cells and moderately expressed in Calu-3 cells. Net secretory transport of 3H-digoxin was observed in both models. This was reduced at 4°C and in the presence of the selective but non specific P-gp inhibitor PSB383 and the multidrug resistance protein (MRP) inhibitor MK571. P-gp specific antibody inhibitor UIC2 and the metabolic inhibitors sodium azide and sodium dichloroacetate had no effect on 3H-digoxin transport in Calu-3 cells.

The presence of active transport mechanisms in cultures of human bronchial epithelial cells was demonstrated, although they differed between the models tested. P-gp was not detected in NBHE cells, in line with observed low gene expression in human lung tissue (Bleasby, K. et al. J Pharmacol Exp Ther 2009; 328:3-9). Its presence in the bronchial epithelium and role in lung protection remains to be elucidated.

Results: There was no evidence of toxic effect in blood biochemical parameters, complete blood counts and gross pathology. Histological evaluation of the heart, kidneys, spleen, liver and pancreas was normal in all groups. However, abnormalities were found on lung pathology. In the high concentration group diffuse alveolar damage, alveolar hemorrhage, pulmonary congestion and severe bolus emphysema were shown, whereas in the low dose group only very mild emphysema was found. It is noteworthy that no signs of morbidity or behavioral changes were observed in all groups.

Conclusions: Very high dose Dextromethorphan inhalations have no biochemical or histopathological toxic effects, but may be toxic to the lungs. However, inhalation dose of 60 mg/kg seems to be safe. These data suggest that treatment with inhaled DM in lower doses may be safe and can be used in humans.

P841 Toxicity and safety of dextromethorphan inhalation in a mouse model prior its use in humans

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Background: Dextromethorphan (DM) is a non narcotic codeine analogue, widely used as antitussive agent. DM is active mostly centrally, but also in lung regions. DM was shown to be effective when given by inhalation in guinea pigs. Oral DM prior bronchoscopy is effective in reducing cough and dyspnea. The use of inhalation of DM could lead to faster beneficial effect of the drug, and to avoidance of oral preparation prior bronchoscopy.

Objectives: To define the toxicity of inhaled DM in a mouse model, using different doses and comparison with sham inhalation.

Methods: Female BALB/c mice, were divided to 4 groups exposed to increasing concentrations of DM solution: normal saline, 60, 90 and 360 mg/kg. Inhalation studies lasted ~ 20 minutes, for 3 weeks. Blood analysis and complete histological evaluation were performed.
P844 Fluticasone furoate, a novel corticosteroid, maintains glucocorticoid receptor nuclear localisation for 24 hours after washout in monocytes

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Background: Fluticasone furoate (FF) is a novel corticosteroid (CS) under development for inhaled once daily administration for chronic obstructive pulmonary disease and asthma. CS act via binding to the glucocorticoid receptor (GR). Upon activation of GR, receptors enter into the nucleus, an essential prerequisite for CS function. In dose-ranging studies in asthmatics, FF had 24 hour (h) duration of efficacy. We hypothesized, therefore, that the sustained activity of FF is due to prolonged GR nuclear translocation.

Method: The effects of FF on GR nuclear translocation over a 24 h time-course was examined in U937 monocytes. In addition, we compared the effect of a 20 h washout on GR nuclear localisation following treatment with FF for 4 h. Statistical analysis was performed using Kruskal-Wallis analysis and results represented as mean±SEM.

Results: FF significantly induced GR nuclear translocation in a time- (2-24h) and concentration- (10^(-11)-10^(-7)M) dependent manner (p<0.05 for each time and concentration measured compared to untreated controls). FF (10^(-7) M) significantly increased nuclear GR levels at 4h (5.4±0.57 fold increase, p<0.05) which was maintained at 16 and 24h. There was a corresponding decrease in cytosolic GR over this time scale. Importantly, in the washout experiments, there was a similar level of GR nuclear translocation at 24h after 4h FF (10^(-7)M) treatment as seen over this time scale. Exposure of cells to FF for 4h as well as 20 h was effective in maintaining the FF induced GR nuclear translocation in a time and concentration dependent manner. Exposure of cells to FF for 4h as well as 20 h was effective as continued exposure for 24h. Funded by GlaxoSmithKline.

P845 Roflumilast N-oxide, a selective PDE4 inhibitor, curbs platelet-leukocyte interactions

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Objective: COPD is associated with cardiovascular comorbidities. Platelet (Pt)-leukocyte interactions play a role in vascular disease. We tested the effect of the PDE4 inhibitor roflumilast N-oxide (RNO), the active metabolite of roflumilast approved for severe COPD in EU, on Pt-mediated neutrophil (Neu) recruitment and expression of TF in Mn.

Methods: Neu adhesion to spread Pt or endothelium (EC) and Pt-induced TF in Mn were analysed with RNO with or without formoterol (F) (100 nM).*p<0.05 vs control (C).

Results: RNO induced TF expression in a time and concentration dependent manner. Exposure of cells to FF for 4h as well as 20 h was effective as continued exposure for 24h. Funded by GlaxoSmithKline.

P846 A-kinase anchoring proteins as novel regulators of airway smooth muscle function

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Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease mainly caused by cigarette smoking (CS). Compartmentalization of CAMP signaling regulates cellular responses to (local) changes in CAM levels. In this respect, the A-kinase anchoring proteins (AKAPs) compartmentalize cAMP signaling by differentially docking proteins involved in cAMP signaling, including β2-adrenergceptors and the cAMP effectors PKA and Epac. Interestingly, AKAP79 (aka AKAP350) involved in β2-adrenergceptor desensitisation, which is opposed by AKAP250 (aka AKAP12). Here we studied the expression pattern and functions of AKAPs in regulating inflammatory cytokine release and the responsiveness to β2-adrenergceptors.

AKAP51, AKAP250 and AKAP50 (aka AKAP9) are expressed in human airway smooth muscle (hASM). Treatment with CS downregulated AKAP250 and (to a lesser extent) AKAP79, but not AKAP450. In lung tissue of COPD patients all these AKAPs were downregulated. In hASM cells, CS-induced IL-8 release was dose-dependently decreased by the β2-agonist fenoterol as well as by direct activation of PKA and (only marginally) of Epac. CS-induced IL-8 release was augmented by the PKA-binding blocking peptide st-H31, a generic AKAP inhibitor. Importantly, in the presence of st-H31 fenoterol was unable to reduce CS-induced IL-8, whereas the PKA activator was still fully effective.

In conclusion, AKAPs are expressed in the airways and coordinate the communication between β2-adrenergceptors and CAMP effectors in order to reduce CS-induced inflammation. AKAP9 expression is altered in COPD. AKAP9s could contribute to the pathophysiology of this disease. Supported by Stichting Astma Bestrijding and a Rosalind Franklin Fellowship.

P847 Bosentan is superior to ambrisentan in reducing the expression of asthma- and COPD-related cytokines

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TNFα substantially contributes to the establishment of chronic airway inflammation. TNFα-induced expression of inflammatory genes in human airway smooth muscle cells (HASMCs) might depend on endothelin-1 (ET-1) signaling. We investigated inflammatory gene expression in TNFα-exposed HASMCs. We compared the anti-inflammatory effects of the non-selective endothelin antagonist Bosentan (ETAR/ETBR antagonist Bosentan with or without formoterol (F) (100 nM).*) p<0.05 vs control (C). The expression of 4,948±3,316 genes was induced twofold or more by TNFα. Among them were GM-CSF, G-CSF, 8 CCR and 8 CXC family members and 5 interferons. Bosentan and Ambrisentan reduced this expression (4,305±53 or 396±63 genes, respectively, in TNFα-exposed HASMCs. Among them were CCL5/7/8/19/20, CCL6/10, CXCL1, IL-6/7/23 and GM-CSF (all p<0.05). The release of CCL2, CCL7, CXCL1 and GM-CSF was more efficiently reduced by Bosentan compared with Ambrisentan (p<0.05). With the exception of GM-CSF, the effects of ET receptor antagonists on these factors were due to inhibition of gene transcription. ETAR/ETBR antagonists contribute to the establishment of chronic airway inflammation in asthma and COPD. Particularly none-selective ET receptor antagonists might have therapeutic utility in early stages of chronic airway diseases by counteracting the establishment of inflammatory processes.

P848 Simvastatin selectively inhibits TSLP-production in primary bronchial epithelial cells from COPD donors

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Background: Possibly reflecting anti-inflammatory properties, statin treatment may ameliorate COPD exacerbations. Viral infections apparently cause TH2 type COPD exacerbations. We have previously shown that thymic stromal lymphopoietin (TSLP), a cytokine linking innate and adaptive immunity and switching on TH2 type inflammation, is overproduced in viral stimulated epithelial cells from patients with GOLD stage II COPD.

Methods: Primary bronchial epithelial cells, obtained by fibre optic bronchoscopy from COPD (n=4) and healthy individual (n=3) donors, were grown in 12-well plates and stimulated with a synthetic viral surrogate, double-stranded RNA (dsRNA, 10μg/ml) to induce cytokine expression (3h, RT-qPCR) and production (24 h, ELISA). Simvastatin (0.2-5μg/l) with or without mevalonate (13g/ml) was added 18 h prior to dsRNA. Alternatively, dexamethasone (1μM) was added 1 h prior to dsRNA.

Results: dsRNA induced TSLP, TNF-α and IL-8 mRNA and protein expression (p<0.05-p<0.001). Simvastatin dose-dependently, but not dexamethasone, inhibited dsRNA-induced TSLP mRNA expression and protein release (p<0.05-p<0.001) in COPD cells. Simvastatin acted independent of mevalonate. dsRNA-induced TNF-α and IL-8 were not inhibited (p<0.05).

Conclusion: Independent of the mevalonate pathway, simvastatin selectively inhibited dsRNA-induced TSLP-production in COPD cells. These data support exploration of statin treatment in viral-induced COPD exacerbations. The pharmacological
Effects of corticosteroid or montelukast associated to iNOS inhibitor on airway remodelling in guinea pigs chronically exposed to cigarette smoke

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Aims: Distal lung alterations have been recently addressed on asthma pathology. We evaluated oxidative stress, actin content, IL and MMP9 positive cells in distal lung parenchyma after montelukast or dexamethasone treatment associated or not to an iNOS inhibitor (400W) in guinea pigs (GP) with chronic inflammation.

Methods: Mice were inhaled with ovalbumin (OVA group 2x/week/4weeks). After 4th inhalation, GP were treated with montelukast (M group 10mg/kg/day) or dexamethasone (D group 5mg/kg/day). 1400W (W group 1mg/kg/day) was given daily in the last 4 days (W, DW and MW groups). After 72 hrs of 7th inhalation, GP were anesthetised, lung strips were submitted to histopathological evaluation.

Results: Isoprostane was reduced in M (9.4 ± 0.4%, D (7.4 ± 0.2%), DW (6.1 ± 0.2%) and W (6.5 ± 0.4%) compared to OVA (14.5 ± 0.2%, P<0.05). Actin content was attenuated in M (7.6 ± 0.5%, D (6.3 ± 0.2%), W (6.2 ± 0.4%) DW (5.4 ± 0.2%) and D (7.2 ± 0.2%) compared to OVA (9.6 ± 0.5%, P<0.05). There was a decrease of IL5+ cells in W (4.8 ± 0.5/10⁴ μm²), M (6.2 ± 0.3/10⁴ μm²), D (4.8 ± 0.5/10⁴ μm²), DW (2.8 ± 0.2/10⁴ μm²) and W (5.0 ± 0.3/10⁴ μm²) compared to OVA (8.2 ± 0.5/10⁴ μm², P<0.05). There was also a reduction of MMP9+ cells in M (6.6 ± 0.4/10⁴ μm²), D (5.4 ± 0.3/10⁴ μm²), W (5.8 ± 0.4/10⁴ μm²), DW (6.2 ± 0.5/10⁴ μm²) and W (4.8 ± 0.4/10⁴ μm²) compared to OVA (9.6 ± 0.5/10⁴ μm²).

Conclusions: In this animal model, corticosteroid or montelukast associated to iNOS inhibitor contributes to the reduction of oxidative stress, actin content MMP9 expression and was efficient to attenuate Th2 cytokine expression in distal lung.

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Effects of aclidinium on cigarette smoke-induced fibroblast activation in vitro

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Aims: To assess the effects of aclidinium bromide, a novel, long-acting muscarinic antagonist, on human lung fibroblast activation after CS exposure in vitro.

Methods: Lung fibroblasts were incubated with aclidinium (10⁻⁷M-10⁻⁵M), the ERK 1/2 inhibitor PD98059 (10μM), the cAMPr analogue dbcAMP (1mM) or the antioxidants N-acetylcysteine (NAC, 1mM) and apocynin (10μg/Ml) for 30 min and then exposed to CS extract (CSE) for 48 h. The collagen type I, αSMA expression and ERK 1/2 phosphorylation were measured by RT-PCR and/or Western blot (WB). Intracellular reactive oxygen species (ROS) were measured by DCFDA fluorescence dye. Protein expression by the NADPH complex gp67phox and choline acetyltransferase (Chat) were measured by WB.

Results: Aclidinium, PD98059, dbcAMP, NAC and apocynin attenuated the CSE-induced increase in αSMA and collagen type I expression. Aclidinium also attenuated the CSE-dependent increase in Phospho-ERK and the CSE-induced increase in ROS to 50% of control. NAC and apocynin fully suppressed the increase in ROS, and PD98059 and dbcAMP reduced it to 20% of control. Aclidinium 10⁻⁵M completely suppressed the CSE-induced increase in gp67phox expression. Aclidinium-induced Chat upregulation suggested an autocrine acetylcholine regulation in response to CSE.

Conclusions: Aclidinium reduces human lung fibroblast activation following CSE exposure in vitro. Aclidinium may reduce lung fibroblast activation in patients with COPD after CS exposure.

Effects of corticosteroid or montelukast associated to iNOS inhibitor on airway remodelling in guinea pigs chronically exposed to cigarette smoke

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Aim: To investigate whether corticosteroids, a novel muscarinic antagonist, reduces airway remodelling in guinea pigs chronically exposed to CS.

Methods: Male guinea pigs (n=46) were divided into 2 groups: control (n=22) and exposed to CS (n=24). 6 cigarettes/day, 5 days/week for 24 weeks. Animals received nebulised vehicle, aclidinium 10μg/mL or aclidinium 30μg/mL 60 min before CS exposure. The thickness of the adventitia, muscularis and internal layers of the airway wall was measured by planimetry in immunostained sections. Epithysma and goblet cell metaplasia were evaluated using sections stained with hematoxylin-eosin and alcian blue, respectively. The internal luminal perimeter of each airway served as a reference to normalise and stratify the assessments.

Results: Aclidinium prevented thickening of the small airway muscularis layer in animals exposed to CS. Thickness after CS exposure was: aclidinium 10μg/mL, 18μm and aclidinium 30μg/mL 21μm vs vehicle 32μm (p<0.05 both doses). Aclidinium (both doses) reduced the amount of smooth muscle content (α-actin) in CS-exposed animals. Thickening of the adventitia and muscular layers, goblet cell metaplasia and epithysma were not significantly reduced with aclidinium treatment.

Conclusions: Aclidinium 10μg/mL and 30μg/mL reduce airway remodelling in guinea pigs by reducing the muscularisation of small airways seen after chronic CS exposure. This study was supported by Almirall S.A., Barcelona, Spain, and Consorcios Estratégicos Nacionales en Investigación Técnica (CENIT).

Effects of aclidinium on respiratory function in guinea pigs chronically exposed to cigarette smoke

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Introduction: Chronic obstructive pulmonary disease is characterised functionally by decreased respiratory function due to airflow obstruction.

Aims: To evaluate the effects of aclidinium bromide, a novel muscarinic antagonist, on respiratory function and signs of bronchial irritation in guinea pigs chronically exposed to cigarette smoke (CS).

Methods: Male guinea pigs (n=46) were divided into 2 groups: control (n=22) and CS-exposed (n=24). 6 cigarettes/day, 5 days/week for 24 weeks. Animals received nebulised vehicle, aclidinium 10μg/mL or aclidinium 30μg/mL 60 min before CS exposure. The thickness of the adventitia, muscularis and internal layers of the airway wall was measured by planimetry in immunostained sections. Epithysma and goblet cell metaplasia were evaluated using sections stained with hematoxylin-eosin and alcian blue, respectively. The internal luminal perimeter of each airway served as a reference to normalise and stratify the assessments.

Results: Aclidinium prevented thickening of the small airway muscularis layer in animals exposed to CS. Thickness after CS exposure was: aclidinium 10μg/mL, 18μm and aclidinium 30μg/mL 21μm vs vehicle 32μm (p<0.05 both doses). Aclidinium (both doses) reduced the amount of smooth muscle content (α-actin) in CS-exposed animals. Thickening of the adventitia and muscular layers, goblet cell metaplasia and epithysma were not significantly reduced with aclidinium treatment.

Conclusions: Aclidinium 10μg/mL and 30μg/mL reduce airway remodelling in guinea pigs by reducing the muscularisation of small airways seen after chronic CS exposure. This study was supported by Almirall S.A., Barcelona, Spain, and Consorcios Estratégicos Nacionales en Investigación Técnica (CENIT).
sure. Compared with CS-exposed non-treated animals, treatment with aclidinium 30μg/mL resulted in a lower increase in Pden after CS exposure (vehicle vs aclidinium 30μg/mL: 110.6±26.7 vs 71.4±32.4; p=0.016). CS exposure resulted in cough episodes and respiratory crises which were attenuated by aclidinium 30μg/mL.

Conclusions: In guinea pigs chronically exposed to CS, aclidinium 30μg/mL improved inflammatory function by significantly reducing the increase in Pden after CS exposure and reducing the development of cough and respiratory crises. This study was supported by Almirall S.A., Barcelona, Spain, and Consorcio Estratègic Nacional en Investigación Tècnica (CENIT).

P854 Protective effect of lecithinized superoxide dismutase (PC-SOD) against elastase-induced pulmonary emphysema in mice
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No medication exists that clearly improves mortality of chronic obstructive pulmonary disease (COPD), an obstructive lung disease. In particular, superoxide anions would play important roles in the abnormal inflammatory response and in pulmonary emphysema, which arises due to an imbalance in proteases and antiproteases and increased levels of apoptosis. Superoxide dismutase (SOD) catalyses the dismutation of a superoxide anion to hydrogen peroxide. Lecithinized SOD (PC-SOD) has overcome a number of the clinical limitations of SOD, including low tissue affinity and low stability in plasma. In this study, we examine the effect of PC-SOD on elastase-induced pulmonary emphysema. The severity of the pulmonary inflammatory response and emphysema in mice was assessed by various criteria, such as enlargement of airspace.

Inhalation of PC-SOD suppressed elastase-induced pulmonary inflammation, emphysema and dysfunction. Inhalation of PC-SOD also suppressed the elastase-induced increase in the pulmonary level of superoxide anions, cell death, activation of proteases and expression of pro-inflammatory cytokines and chemokines. We also found that inhalation of PC-SOD suppressed cigarette smoke-induced pulmonary inflammation.

The results suggest that PC-SOD protects against pulmonary emphysema by inhibition of inflammation and cell death and amelioration of the protease/antiprotease imbalance. We propose that inhalation of PC-SOD would be therapeutically beneficial for COPD.

P855 Prevention of adverse pulmonary consequences of myocardial ischaemia in rats
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The efficacy of treatment strategies against airway hyperresponsiveness (AHR) were compared following chronic postcapillary pulmonary hypertension induced by myocardial ischaemia (MI). Airway resistance (Raw) was measured in four groups of rats under baseline conditions, and following iv infusion of 2-18 μg/kg/min methacholine (MCH). Sham surgery was then performed in Group C, while the left interventricular coronary artery was ligated in the other groups without treatment (Group I), or daily treatments with combined angiotensin enzyme converter (ACE) inhibitor and diuretics (enalapril, lasix, Group IE), or a calcium channel blocker (diltiazem, Group ID). Eight weeks later, MCH provocations were repeated. Equivalent dose of MCH causing 50% increase in Raw (ED50) was determined. Left atrial pressure (Pla) was estimated from the end-diastolic left ventricular pressure. Elevations in Pla to MI (6.8±1.1 [SD] vs. 15.2±1.3 mmHg in Groups C and IE, respectively) were not affected by the treatment in Group ID (13.7±3.1 mmHg), whereas they were inhibited in Group IE (10.9±3.2 mmHg, p=0.005). The development of AHR following MI was completely abolished in both Groups ID and IE.

Conclusion: In guinea pigs chronically exposed to CS, aclidinium 30μg/mL improved inflammatory function by significantly reducing the increase in Pden after CS exposure and reducing the development of cough and respiratory crises. This study was supported by Almirall S.A., Barcelona, Spain, and Consorcio Estratègic Nacional en Investigación Tècnica (CENIT).

P856 Can streptomycin prevent the selection of isoniazid-resistant mutants in nude mice infected with M. tuberculosis?
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Rationale: In a previous study, the treatment of M. tuberculosis infected athymic nude (nude) mice with the bactericidal drug isoniazid (H) combined with the two steroiding drugs, rifampicin (R) and pyrazinamide (Z) failed and selected H-resistant mutants. We investigated whether the combination of H with the bactericidal drug, streptomycin (S) would be able to prevent that selection.

Methods: A total of 80 nude mice were aerosol infected with 3.67×10^3 log cfu of M. tuberculosis H37Rv. Two weeks later, at treatment initiation, mice were randomized in the following subgroups: untreated and treated with RZH+ethambutol (E) as controls; treated with S, R, H, R, H+streptomycin. These groups received streptomycin 50 μg/d for 5 days/week/days for 12 weeks. Drug doses (mg/kg) were 10 for R and H, 150 for S and 100 for E. Lung CFU counts were done the day after infection, on treatment initiation, and after 4, 8 and 12 weeks of treatment on plain and H 0.2 μg/ml-containing 7H11 selective plates.

Results: Lung CFU counts were 7.40±0.28 log10 on treatment initiation. After 4, 8 and 12 weeks of treatment, they were 5.82±0.35, 4.05±0.55 and 2.30±0.25, respectively for RZHE; 5.00±0.90, 5.32±0.69 and 5.05±0.90, respectively for SH; and 6.00±0.39, 6.24±0.28, 7.68±0.49, respectively for RH. H resistance was prevented in RZHE treated mice but not in SH and RH treated mice.

Conclusion: Despite its bactericidal activity, S alone cannot prevent selection of H-resistant mutants in nude mice.

P857 Soluble guanylate cyclase stimulator riociguat prevents fibrotic tissue remodeling and improves survival in salt-sensitive Dahl rats
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Direct stimulation of soluble guanylate cyclase (sGC) is an emerging therapeutic approach to the management of cardiopulmonary disorders associated with endothelial dysfunction. Novel sGC stimulators, including riociguat, aim to have a dual mode of action: they sensitize sGC to endogenously produced nitric oxide (NO) and also directly stimulate sGC independently of NO. Little is known about their effects on tissue remodeling and degeneration and survival in experimental malignant hypertension. Mortality, hemodynamics and biomarkers of tissue remodeling and degeneration were measured in Dahl salt-sensitive rats maintained on a high salt diet and treated with riociguat (3 or 10 mg/kg/d) for 14 weeks. Riociguat markedly attenuated systolic hypertension, improved systolic heart function and increased survival. Histological examination of the heart and kidneys revealed that riociguat significantly ameliorated fibrotic tissue remodeling and degeneration. Correspondingly, mRNA expression of the pro-fibrotic biomarkers osteopontin (OPN), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and plasminogen activator inhibitor-1 (PAI-1) in the myocardium and the renal cortex was attenuated by riociguat. In addition, riociguat reduced plasma and urinary levels of OPN, TIMP-1, and PAI-1. Riociguat markedly improves survival and attenuates systemic hypertension and systolic dysfunction, as well as fibrotic tissue remodeling in the myocardium and the renal cortex in a rodent model of pressure and volume overload. These findings suggest a therapeutic potential of sGC stimulators in providing organ protection in diseases associated with impaired cardio-renal functions.

P858 AZD3199: A fast acting β2-receptor agonist with a long duration of action
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Background: AZD3199 is a novel, ultra long acting β2-agonist (uLABA) designed to combine 24 hour duration of action with a fast onset of action similar to formoterol, as well as low systemic exposure. Its profile was evaluated in the guinea pig.

Methods: Bronchoconstriction was elicited in anesthetized guinea pigs by histamine administration. Dose-response curves for AZD3199 given via the intravenous and intratracheal (i.t.) routes were constructed and sub-maximal doses used to define duration of action from 2–72 hours. The β-antagonist propranolol was administered after histamine-challenge to show the level of β2-eficacy at each dose and time point. Blood samples were taken throughout and plasma K+ concentrations used as a marker of systemic β2 effects. Satellite groups were used to monitor
lung and plasma AZD3199 levels. The pharmacodynamic and pharmacokinetic profiles of AZD3199 were compared to formoterol and salmeterol.

**Results:** Sub-maximal doses of AZD3199 given i.t. inhibited bronchoconstriction for 24 hours; equi-effective doses of formoterol and salmeterol had significant effects for 12 hours. AZD3199 had the longest lung PK half-life. Inhalation of sub-maximal doses of nebulized AZD3199 gave bronchoprotection lasting 24 hours, with no significant effects on blood K⁺ levels. An equi-effective inhaled dose of formoterol bronchoprotected for 8 hours with decreases in blood K⁺ seen at 2 hours. The reduced systemic effects for AZD3199 relative to formoterol are consistent with its high lung to plasma concentration ratio.

**Conclusion:** AZD3199 is a novel d/LABA with a fast onset of action and a longer duration of action than conventional LABAs, and also has a low potential for cardiovascular side effects.

**PS89**

An assessment of the functional profile of aclidinium in human bronchi and left atria

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**Introduction:** Aclidinium bromide is a novel, long-acting muscarinic antago-
nist, currently in development for the treatment of chronic obstructive pulmonary disease.

**Aims:** To assess the functional profile of aclidinium in isolated human bronchi and left atria, the organs responsible for efficacy and systemic side effects, respectively. Methods: The smooth muscle relaxant effects of aclidinium, tiotropium and ipra-
ropium were measured in isolated human bronchial rings by determining potency, onset (time to 50% inhibition) and offset (time to 50% recovery). The effects of the muscarinic agonists were standardised in human left atria strips pre-treated with carbachol 10μM to inhibit electrically-induced contractions through the M3 receptor. Duration of action was defined as the time required to recover 50% of the carbachol effect.

**Results:** Aclidinium had similar potency to tiotropium and ipratropium in human bronchi. Aclidinium onset (4.4±0.7 min) was faster than tiotropium (7.4±1.3 min; p<0.05) and similar to ipratropium (3.3±0.6 min). Aclidinium offset (334±49 min) was longer than tiotropium (76±9 min; p<0.05). Tiotropium did not recover within 10 h. Aclidinium inhibited the bradykininergic effect of carbachol in human left atria, with a shorter half life (110±2 min; 95% confidence interval [CI] 103.0, 117.3) than tiotropium (159.3 min; 95% CI 148.2, 171.7) but longer than ipratropium (16.6 min; 95% CI 16.4, 16.8).

**Conclusions:** Aclidinium has similar potency but faster onset of action than tiotropium in human bronchi. In human left atria, aclidinium had a shorter duration of action than atropine at M3 receptors, suggesting a lower potential for cardiovascular side effects.

**96. Bronchodilators in asthma and COPD**

**P860**

Efficacy of indacaterol is maintained irrespective of inhaled corticosteroid (ICS) use

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**Introduction:** Indacaterol is a once-daily inhaled β2-agonist bronchodilator for COPD.

**Aim:** Pooled analysis to determine indacaterol efficacy in subgroups of COPD patients (pts) receiving ICS or not.

**Methods:** Data from 4088 pts with moderate-to-severe COPD in 3 randomised, double-blind, placebo-controlled studies of indacaterol 150 and 300μg od, tiotropium 18μg od (open-label), formoterol 12μg bid & salmeterol 50μg bid were pooled: 44% of pts had baseline ICS use, 56% no ICS use. Endpoints at 6 months: trough FEV1, transition dyspnoea index (TDI) and St George’s Respiratory Questionnaire (SGRQ) total scores. The % of pts with clinically important difference in TDI and SGRQ were analysed as odds ratios (OR).

**Results:** Differences vs placebo (n=661) not on ICS, 524 on ICS (p<0.05, ¶p<0.01, ||p<0.001) in pts not on ICS (‘no’) or on ICS (‘ICS’) (p<0.05 vs tiotropium, ‡p<0.05 vs formoterol, §p<0.05 vs salmeterol, †¶p<0.05 vs indaceterol 150μg).

**Conclusions:** Indacaterol improved FEV1, & clinical outcomes after 6 mo irrespective of COPD severity. Indacaterol 300μg was notably effective for breathlessness in the more severe subgroup.

**P862**

The efficacy of the assistant use of short-acting β2 stimulant procaterol on the daily activity in COPD patients. Niigata multicenter study

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**Background and purpose:** COPD patients have some dyspnoea on exertion in spite of medication. Guidelines suggest the use of short-acting β2 antagonist (SABA) as necessary. There are few reports to see whether the supplementary use of SABA inhalation impairs their physical activity, ADL, and QoL in the daily life. We evaluated the efficacy and safety of assistant use of procaterol inhalation.

**Methods:** COPD patients were enrolled and asked to keep as active as possible. Physical activities were measured by the uni-axial accelerometer. COPD patients were divided into two groups. One was the group as controls (Group C) and the other was the procaterol group (Group P).

**Results:** Aclidinium improved FEV1, and clinical outcomes after 6 months in patients not receiving ICS and those on ICS.
other was those who used procaterol before or after the exertion when they felt
dyspnoea (Group P). Physical activities, ADL and QoL in the daily life were com-
pared during the observational and the experimental periods for each one month.
Statistical analyses were done by two-way ANOVA. A p < 0.05 was considered
significant.

**Results:** Forty four patients were enrolled and 37 completed the study.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Group C</th>
<th>Group P</th>
</tr>
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<tbody>
<tr>
<td>M/F</td>
<td>19/0</td>
<td>162 n.s.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73.5±5.7</td>
<td>69±6.7</td>
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<tr>
<td>%FEV1 (%)</td>
<td>72.6±11.5</td>
<td>51±17.1</td>
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</tbody>
</table>

Average steps per day

<table>
<thead>
<tr>
<th>Group</th>
<th>5659±3267</th>
<th>5314±3436</th>
<th>5230±3313</th>
<th>5453±3013</th>
<th>54 35±303</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild level of physical activity (%)</td>
<td>24.6±7.4</td>
<td>22.6±7.6</td>
<td>27.4±11.1</td>
<td>28.1±11.3</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Ob.: observational period; EX: experimental period.

And validity domain of the SF-36 improved in Group P during the experimental period.

**Conclusion:** The assistant use of SABA inhalation may maintain the mild level of physical activity and increase validity in the daily life in COPD patients.

**P863**

**Onset of action and effect of withdrawal of roflumilast in COPD**

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**Background/Rationale:** Roflumilast (ROF) is an oral, selective phosphodiesterase 4 inhibitor licensed for the maintenance treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations. It improves lung func-
tion and reduces the rate of exacerbations in these patients. Limited data are available on the on- and off-action of ROF and the effects of treatment withdrawal.

**Methods:** Patients aged 40–75 years with stable COPD, fixed airways obstruction, post-bronchodilator FEV1 ≥70% predicted and ≥10 pack-years smoking history were randomised to one of 3 groups: once-daily ROF 500 μg for 24 weeks, once-daily placebo (PBO) for 24 weeks, and ROF 500 μg for 12 weeks then PBO for 12 weeks (ROF/PBO).

**Results:** A total of 581 patients were randomised (ROF, n=200; PBO, n=186; ROF/PBO, n=195). Demographic and baseline characteristics were similar in all groups. FEV1 increased with ROF: at weeks 1, 4, 8, and 12 least squares mean change in trough FEV1 at 24 hours were reported at doses 12.5 μg to 400 μg were well tolerated. ROF/PBO demonstrated rapid onset of bronchodilation with clinically meaningful improvements in lung function over 24 hours following nebulization in patients with COPD.

**Conclusion:** Single doses of EP-101 ranging from 12.5 μg to 400 μg were well tolerated. EP-101 demonstrated rapid onset of bronchodilation with clinically meaningful improvements in lung function over 24 hours following nebulization in patients with COPD.

**Funded by:** Elevation Pharmaceuticals Inc.

**P864**

**Doxofilline: Efficacy and safety in complex treatment of COPD**

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**Aim of study:** To evaluate efficacy and safety of Aerofylline, ABC Farmaceutici (doxofilline) in patients with stable COPD.

**Study population and methods:** 30 out-patients (pts) with stable COPD, stage II were divided on two groups: 15 pts (11 men, mean age 47.5±8.6 yrs) treated with inhaled bronchodilators and doxofilline 400 mg bid (Group 1) and 15 pts (12 men, mean age 50.3±9.0 yrs), treated with inhaled bronchodilators only (Group 2). Pulmonary function tests, respiratory muscles fatigue (by MasterLab. Jager), Holter ECG and dyspnoea (by MRC score) were evaluated in all pts before and 30 days after start of treatment.

**Results:** Both groups were similar regarding to age, sex, duration of disease, FEV1, Pmax, and dyspnoea level at the beginning of treatment. 30 days after start of treatment the results were following: FEV1 did not change statistically significant in both groups. At the same time, dyspnoea score decrease significantly in Group 1 but not in Group 2 (down to 0.4±0.4 scores and 1.9±0.5 scores respectively). Pmax in Group 1 increase on 21.3%, in Group 2 – on 11.9%. We did not find any difference in tachycardia and prematurity beat rate between the groups.

**Conclusions:** Doxofilline did not improve pulmonary function, but significantly decrease respiratory muscles fatigue and dyspnoea in patients with COPD, stage II. Doxofilline did not influence significantly on a heart rhythm.

**P865**

**Efficacy and safety of nebulized glycopyrrrolate (EP-101) for administration using high efficiency nebulizer in patients with COPD**

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**Introduction:** EP-101 is a long-acting muscarinic antagonist formulation of gly-
copyrrrolate optimized for nebulization in development for the treatment of COPD.

This dose-ranging study assessed the efficacy and safety of single doses of nebulized EP-101 in patients with COPD.

**Methods:** This was a randomized, double-blind, placebo-controlled, 6-period cross-over study in 42 patients with moderate-to-severe COPD. Patients were randomized to receive single doses of EP-101 (12.5, 50, 100, 200 and 400 μg) and placebo via a high efficiency nebulizer, with a 5–12 days of washout between treatments. Plasma PK was assessed in a subset of patients.

**Results:** The study patients had a mean age of 62 years, COPD duration of 7 years, post-bronchodilator FEV1 of 54% predicted normal, FEV1/FVC of 44.9%, FEV1 reversibility of 27.3%. All treatments were well tolerated with similar AE rates between all treatments and no clinically relevant changes in vital signs (heart rate, systolic and diastolic blood pressure) and ECG parameters including QTc interval. Following treatment with EP-101 at all doses there was a rapid bron-
chodilatory response at 5 minutes. Statistically significant improvements in mean change in trough FEV1 at 24 hours were reported at doses ≥50 μg compared with placebo (37mL, 72mL, 104mL, 118mL and 95mL at doses 12.5, 50, 100, 200 and 400 μg, respectively).

**Conclusion:** Single doses of EP-101 ranging from 12.5 μg to 400 μg were well tolerated. EP-101 demonstrated rapid onset of bronchodilation with clinically meaningful improvements in lung function over 24 hours following nebulization of 400 μg in patients with COPD.

**Funded by:** Elevation Pharmaceuticals Inc.
P668
Efficacy and safety of AZD3199, an inhaled ultra-long-acting β2-agonist, in patients with COPD.

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Objectives: To study the efficacy and safety of three once-daily doses of AZD3199 inhaled via Turbuhaler compared with twice-daily formoterol and placebo over 4 weeks in COPD patients.

Methods: This was a 4-week randomised, double-blind, parallel-group multi-centre Phase II study to compare once-daily inhaled doses of AZD3199 (200, 400 and 800 μg delivered) with formoterol (9 μg bid) and placebo in 329 adults with moderate/severe COPD (NCT00927084). Bronchodilation was assessed by average post-dose FEV1 values from 0–4 hrs (E0_4), peak FEV1 and FEV1 values from 24–26 hrs (E24_26) post-dose. Use of β2-agonist reliever medication, salbutamol reversibility, symptom scores (CCQ) and safety were also assessed.

Results: A total of 822 patients (mean age 63.9 yrs; post-bronchodilator FEV1 [G]; 59.0 ± 22.2% of predicted) were randomised to receive one of the four treatment regimens; 208 patients in each group over the study period. Sex, Age and smoking history were used as covariates. We observed lung function (FEV1% pred) a 1.03 ± 0.31 point increase was observed in the formoterol group compared with placebo (0.67 ± 0.31 point increase in placebo after 4 weeks’ treatment). Each symptom (cough, sputum production and dyspnea) was evaluated on a 4-point scale by the patients.

Conclusion: AZD3199 is well tolerated with no safety concerns.

Conclusions: AZD3199 is a safe and effective uLABA with a 24-hour duration of action.

P870
Influence of tiotropium bromide on airway inflammation and symptom in COPD patients

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Aim: Chronic obstructive pulmonary disease (COPD) is characterized by abnormal inflammatory response of lungs to noxious particles or gases. The aim of this is to study the impact of tiotropium bromide treatment on airway inflammation and symptoms in COPD patients.

Methods: Tiotropium bromide treatment with 18 mcg daily dose, was started in newly diagnosed, consecutive mild–moderate stable COPD patients. Peroxynitrite, interleukin-6 (IL-6), 8-isoprostane and tumour necrosis factor-alpha (TNF-α) were measured in the expired breath condensate fluid before the treatment and at the end of first month. Each symptom (cough, sputum production and dyspnea) was evaluated on a 4-point scale by the patients.

Results: Twenty-two patients (81% men), with a mean age 65.4±10.1 years were included in the study. The mean nitrotyrosine and 8-isoprostane levels for oxidative stress marker in BEC before and after treatment were 4.5±2.3, 3.5±1.9 pg/ml (p=0.006) and 7.3±10.8, 8.1±11.7 pg/ml (p=0.3) respectively. The mean TNF-α, IL-6 and 8-isoprostane levels were measured in the expired breath condensate fluid before the treatment and at the end of first month. Each symptom (cough, sputum production and dyspnea) was evaluated on a 4-point scale by the patients.

Conclusion: There were no significant changes for inflammatory and oxidative stress markers in expired breath condensate fluid after a tiotropium treatment of one month, but tiotropium treatment helps to control symptoms in COPD with an increase in FEV1.

P871
The impact of tiotropium on mortality when added to inhaled corticosteroids and long-acting beta agonist therapy in COPD

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Background and objectives: Tiotropium (TIO) has been shown to improve lung function, quality of life and reduce mortality and exacerbations in COPD. However it remains unclear whether such benefits are seen when TIO is used in conjunction with inhaled corticosteroids (ICS) plus long acting beta-2 agonists (LABA).

Methods: Retrospective Cohort study using linked NHS databases on hospital admissions, COPD outcomes, prescribing and mortality. Cox proportional hazard regression analysis was used to assess the association of TIO with ICS+LABA on mortality and exacerbations. History of respiratory and cardiovascular disease, Sex, Age and smoking history were used as covariates. We observed lung function in each group over the study period.

Results: 3004 COPD patients were included in the study. 2082 patients were prescribed ICS+LABA+Tio and 922 were prescribed ICS+LABA. Mean follow-up was 4.65 years. Mean age 68.5 years. 1035 patients died during the study. The adjusted hazard ratio for all-cause mortality for ICS+LABA+TIO vs ICS+LABA was 0.67 (95% CI 0.58-0.76) p<0.001. Adjusted hazard ratios for respiratory hospital admissions and oral corticosteroid use were 0.86 (95% CI 0.74-0.99) p=0.043 and 0.72 (95% CI 0.65-0.81) p<0.001. In the ICS+LABA group (mean FEV1% pred 66.8%), mean first and last FEV1 and FVC (L) were 1.56 ± 1.37 and 2.64 ± 2.72. In the ICS+LABA+TIO group, (mean FEV1% pred 51.6%), mean first and last FEV1 and FVC (L) were 1.24 ± 1.20 and 2.47 ± 2.50.
Conclusions: We have shown that the addition of TIO to ICS+LABA reduces all-cause mortality in our COPD population. Reductions in COPD exacerbations and oral steroid use reaffirm findings of previous studies.

P872
Assessments of protective effects of tiotropium bromide against methacholine- and neurokinin A-induced bronchoconstriction in patients with asthma
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Rationale: Previous studies using short-acting anticholinergics have suggested a possible protective effect on bronchoconstriction induced by the sensory neuropptide neurokinin A (NKA).
Aim: To assess the effect of tiotropium bromide, a long-acting anticholinergic agent, on NKA-induced bronchoconstriction.
Methods: PC20 NKA and PC20 methacholine were investigated in asthmatic patients after 20 days of treatment with tiotropium bromide (18 µg/gid) or placebo. PC20 was expressed in log2 doubling concentrations (DC). Values were reported as median with 25th-75th percentiles. Fairly comparisons of the log2 PC20 values at screening and at the end of active and placebo treatments were performed.
Results: 16 patients with asthma (9 male; age: 24 (18-63) years) were included. PC20 NKA was 0.18 (0.06 - 0.29) µmol/ml at screening, 0.34 (0.09 - 3.34) µmol/ml after tiotropium placebo, and 0.77 (0.08 - 3.34) µmol/ml after tiotropium bromide. PC20 methacholine was 0.5 (0.3 - 0.7) mg/ml at screening, 0.3 (0.2 - 1.5) mg/ml after placebo, and 256.0 (11.7 - 256.0) mg/ml after tiotropium bromide. Differences between active treatment and screening log2PC20 were 2.4 (0.4 - 3.2) DC for NKA (p = 0.06) and 7.6 (4.8 - 9.0) DC for methacholine (p < 0.0001). Differences between placebo treatment and screening for log2PC20 NKA and log2PC0 methacholine were not observed.
Conclusions: Inhaled tiotropium bromide protects against methacholine-induced bronchoconstriction, but not against bronchoconstriction induced by NKA, suggesting that cholinergic mechanisms are not involved in the contractile effects of NKA in patients with asthma.

P873
ACCORD COPD I: Improvements in nighttime symptoms and rescue medication use in COPD with twice-daily aclidinium bromide
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Introduction: Nighttime symptoms in COPD patients can reduce quality of life. In this Phase III study, nighttime symptoms and rescue medication use were assessed in a twice-daily (BID) treatment with aclidinium bromide, a long-acting muscarinic antagonist in development for COPD.
Methods: In this 12-week, double-blind study, COPD patients (FEV1 <70%) were randomised (1:1:1) to aclidinium 200 µg, 400 µg, or placebo. Nighttime symptoms were recorded daily using electronic diaries via a COPD Nighttime Symptoms Questionnaire, which assessed frequency and severity of symptoms and their impact on activity and sleep. Rescue medication use was also assessed.
Results: Of 561 randomised patients, 467 completed the study. At Week 12, aclidinium 200 µg and 400 µg reduced nighttime symptom frequency vs placebo (p = 0.005 and p < 0.005, respectively). Both aclidinium doses reduced severity and impact of nighttime breathlessness and cough on morning activities vs placebo (p < 0.01 and p < 0.05, respectively). Severity of early morning breathlessness and activity restriction due to breathlessness were reduced with aclidinium 200 µg (p < 0.01) and 400 µg (p < 0.001) vs placebo. Compared to placebo, 24-h sputum production was significantly reduced with the 200 µg (p = 0.005) and 400 µg (p = 0.001) doses at Week 12 but not sputum production during sleep. Aclidinium 400 µg improved the severity and impact of breathing symptoms on sleep vs placebo at 12 weeks (p < 0.01). Both aclidinium doses reduced total daily rescue medication use vs placebo (p < 0.001 for both).
Conclusions: Aclidinium 200 µg and 400 µg BID significantly reduced nighttime early morning symptoms and daily rescue medication use.

P874
Improvement in symptoms and rescue medication use with aclidinium bromide in patients with chronic obstructive pulmonary disease: Results from ACCORD COPD I
Alvar Agustí1, Paul W. Jones1, Eric Bateman1, David Singh1,4, Rosa Lamarca1, Gonzalo de Miquel1, Cynthia Caracta2, Esther Garcia Gil1,3.1Thorax Institute, Hospital Clinic and CIBER Enfermedades Respiratorias and Fundació Cuabt-Cimera, Barcelona, Spain; 2St George’s, University of London, London, United Kingdom; 3Thorax Institute, Hospital Clinic and CIBER Enfermedades Respiratorias and Fundació Cuabt-Cimera, Barcelona, Spain; 4Clinical Development, Forest Research Institute, NJ, United States
Introduction: Aclidinium bromide is a long-acting muscarinic antagonist in development for treatment of COPD. In this Phase III study, the effects of twice-daily aclidinium on health outcomes were assessed.
Methods: In this 12-week, double-blind study, moderate to severe COPD patients were randomised to receive aclidinium 200 µg, 400 µg or placebo BID. Health outcomes were assessed monthly via SGRQ and TDI.
Results: Of the 561 patients randomised, 467 (83%) completed the study at Town, South Africa; 6Medicines Evaluation Unit, University of South Manchester, Manchester, United Kingdom; 7R&D Centre, Amtrill, Barcelona, Spain; 8Clinical Development, Forest Research Institute, NJ, United States
Introduction: The ACCORD study investigated the efficacy and safety of two twice-daily doses of aclidinium bromide, a long-acting muscarinic antagonist, in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Methods: In this 24-week, double-blind trial, 828 patients were randomised (1:1:1) to twice-daily aclidinium (200 µg or 400 µg) or placebo. COPD symptoms were assessed using the Transition Questionnaire (TDQ), patient-reported daily electronic diaries and Total Exact score. Rescue medication use was also assessed.
Results: Baseline characteristics were similar between the groups; FEV1% predicted 56.8±12.8%, focal BDI 8±6±2.1. More patients treated with aclidinium 200 µg or 400 µg had a clinically meaningful improvement in TDI focal score (≥2 unit) vs placebo at Week 24 (53.3% and 56.9% vs 45.5%; p=0.032 and 0.004, respectively). Aclidinium dose-dependently improved TDI focal score at Week 24, which was clinically meaningful for aclidinium 400 µg (1.0 unit) and statistically significant for both doses vs placebo (200 µg, p<0.05; 400 µg, p<0.001). Over the study period, aclidinium (both doses) was associated with a lower incidence of night-time (p<0.0001) and early morning (p<0.05) COPD symptoms, a greater reduction in Total Exact score (p<0.0001) and more days without reliever medication (p=0.0003) vs placebo.
Conclusions: Aclidinium 200 µg and 400 µg twice-daily provided statistically significant and clinically meaningful improvements in COPD symptoms in patients with moderate to severe COPD. This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratorie, Italy, New York, USA.
baseline, the mean (SD) pre-bronchodilator FEV₁ and percent predicted were 1.36 (0.54) L and 47.2 (14.1%) respectively. Baseline mean (SD) SGRQ total score and BDI focal score were 46.5 (17.1) and 6.4 (2.1) respectively. Adjusted mean difference was 2.06 (0.32) change from baseline in SGRQ total score at Week 12 were -2.7 (p<0.01) and -2.5 (p<0.02) for aclidinium 200 μg and 400 μg, respectively. At all time points, statistically greater percentages of aclidinium patients achieved clinically significant improvements in SGRQ vs placebo (>24 points; p<0.05 for all except Week 12, 400 μg group). Both aclidinium doses provided significant improvements vs placebo in TDI focal score (p<0.05, range 0.6-0.74) throughout the study; with the exception of aclidinium 200 μg at Week 8 (p<0.06). Significantly greater percentages of patients achieved clinically meaningful improvements in TDI (>1 unit) with both aclidinium doses at all time points vs placebo (p<0.05).

Conclusions: In this 12-week study, aclidinium 200 μg and 400 μg BID significantly improved quality of life and reduced dyspnea for patients with moderate to severe COPD.

**P87**

Aclidinium bromide in patients with chronic obstructive pulmonary disease: Improvement in health status in ATTAIN

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**Introduction:** The ATTAIN study investigated the efficacy and safety of two twice-daily doses of aclidinium bromide, a long-acting muscarinic antagonist, in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

**Methods:** In this 24-week, double-blind, randomized, double-blind study, 2,250 patients (1,126 males) were included. Each patient had moderate to severe COPD (FEV₁ ≤ 50% predicted). All patients were randomized (1:1:1:1) to receive aclidinium (200 μg or 400 μg) or placebo, twice-daily. Health status was assessed using the St George's Respiratory Questionnaire (SGRQ) and the EuroQol Questionnaire (EQ-SD; both the weighted health status index and the visual analogue scale [VAS]).

**Results:** There were 819 patients in the intent-to-treat population; forced expiratory volume in 1 second [FEV₁] % predicted ranged from 46.8±12.8%, baseline SGRQ total score 46.3±16.8 units. At Week 24, 26 patients had a clinically significant improvement in SGRQ total score (decrease ≥ 4 units) with aclidinium 200 μg and 400 μg than placebo (54.9% and 54.3% vs 39.5%; p=0.004 and 0.0014, respectively). At Week 24, the improvement with aclidinium 400 μg was 4.3 units, p<0.0001. SGRQ domain scores (Symptoms, Activity, Impacts) were also significantly improved with both doses vs placebo at Week 24 (p<0.05 all domains). Aclidinium 200 μg and 400 μg also improved the EQ-SD weighted index and VAS compared with placebo at Week 24; the 400 μg dose reached statistical significance for the weighted index (p=0.041) and VAS (p=0.005) vs placebo.

**Conclusions:** Aclidinium 200 μg and 400 μg twice-daily demonstrated statistically and clinically significant improvements in health status.

This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

**P88**

The WHO classification of severe asthma in intensive care patients

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In 2010 a WHO consultative group proposed a definition of severe asthma (JACI 2010; 126:926-3). We have applied this classification to a series of adult patients managed in the intensive care units of 3 large urban hospitals. Over a 5yr period (2006-2010), we registered 386 intensive care admissions for asthma in 332 patients. Their mean age was 53 (18yrs); 57% were women, 48% Chinese, 27% Malays and 14% Indian. Mechanical ventilation was needed in 82% and there were 26 deaths. According to the WHO classification method, the severe asthma, in the first 127 patients, was: untreated in 81 (64%); difficult-to-treat in 41 (32%) and treatment-resistant in 5 (4%). These 3 groups of patients corresponded to distinct and recognizable clinical phenotypes with implications for asthma intervention plans. The untreated patients were from primary care and not attending regular reviews nor receiving long-term control medications. The difficult-to-treat patients were characterized by co-morbidities, non-adherence and under-treatment. We need more effective interventions to reduce the burden of severe asthma at the primary care level. Sub-optimal treatment appeared to be the main barrier to asthma control. Genuine treatment-resistant asthma was an uncommon problem.
Comparison of efficacy of grippe vaccination in asthma and COPD patients

Goran Andonovski1, Zoran Stojanovski2.

Objective: To compare the efficacy of the seasonal grippe vaccination in asthma and COPD patients.

Material and methods: We evaluate the number of exacerbations and number of hospitalisations in 48 subjects in 2 stages and 3 (moderate/severe) COPD and 45 subjects with mild persistent and moderate persistent Asthma in 6 months period. All of them received grippe vaccination before winter. An equal number of COPD and asthma subjects were evaluated like controls. They were not immunized against seasonal influenza. The both groups were matched by sex and age, and receive steroid inhalers (asthmatics), and salbutamol (COPDs) regularly.

Results: Treatment, compliance, lung function, and grippe follow-up appointments. In total, 130 primary care clinics across Denmark participated.

Conclusion: At the initial visit (baseline), 722 patients (37.3%) were classified as well-controlled, 759 (39.2%) as partly controlled and 456 (23.5%) as uncontrolled. At the time of data analysis (September 2011), 641 patients had been offered a both a baseline and a follow-up visit. A higher level of asthma control was found at the follow-up visit compared to the baseline visit (uncontrolled asthma 29.7% and 6.2%, respectively, p<0.001). At the time of the follow-up visit 50% of those partly controlled and 52% of those with uncontrolled asthma had changed from SABA only to ICS (p<0.001). The level of lung function also improved from the baseline to the follow-up visit.

Conclusion: Although most asthmatic individuals received asthma treatment, a substantial number still were partly or poorly controlled. The overall asthma control improved significantly when a systematic asthma management approach was introduced by educated health care staff.

Is mild asthma outside the guidelines?

Olga Valkh1, Vitaly Kuparev2, Julia Bogdanova1. 1Pulmonology Department, Samara Regional Hospital, Samara, Russian Federation; 2The Chair of General Practice, Samara State Medical University, Samara, Russian Federation

The majority of mild asthma cases, its low level of adherence and asthma control had induced investigators examine this cohort. The aim was to study specificity of adherence and asthma control level of patients with mild persistent asthma determined by treatment regimen.

131 patients with mild persistent asthma were examined (age 43.2±15.6 yrs). Two groups were formed:1-st group - had regular inhaled corticosteroids (ICSs) treatment for 3 months (n=57), 2nd - had actual intermittent ICSs therapy (n=74). The questionnaire collects information concerning educational level, social status, knowledge about asthma, FEV1, inflammation parameters (such as Ig E), asthma control, compliance level, etc. 62 patients took part in educational asthma program. We observed uncontrolled asthma in 61.8% of cases. Marker of allergic inflammation - Ig E - had been ranging between 58.8 to 329.4 Ml/ml. There were significant correlations between ACT™ score and patients’ knowledge about asthma (p=0.52, p<0.05). There was no significant difference in asthma control and FEV1 data between two groups. Patients with regular therapy had significantly higher ICSs current dose, compliance index level, more often made planned visits to their physician (p<0.05).

Table 1. Distinctions between mild persistent asthma groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1st group (n=57)</th>
<th>2nd group (n=74)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma control by ACT test</td>
<td>19.7</td>
<td>18.7</td>
<td>0.518</td>
</tr>
<tr>
<td>FRY 1 data</td>
<td>97.6</td>
<td>87.1</td>
<td>0.814</td>
</tr>
<tr>
<td>ICSs current dose</td>
<td>328.75</td>
<td>150.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Compliance Index</td>
<td>66.7</td>
<td>51.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Take part in the educational program</td>
<td>84.1</td>
<td>51.8</td>
<td>0.000</td>
</tr>
</tbody>
</table>

We revealed that mild persistent asthma needs regular control visits to physician, taking part in educational asthma program (electronic one more often), plan of self-management in order to improve adherence and asthma control.
Introduction: Asthma is associated with morbidity and mortality in patient referred to emergency department (ED). Our study was focused on simple objective measures in ED to predicting factors affecting disposition of patients with acute asthma referred to emergency ward.

Methods and materials: Data were collected prospectively at one center over 12-month period on 103 adult patients. Asthma step severity categorization and management was determined by GINA guidelines. Presenting ED vital signs, GSK values, pulmonary function testing (spirometry, flow-volume loop, Pmax, PEmax) and disposition were recorded for each study subject.

Results: In this study 103 patients were studied. In our patients 56 cases (%54.4) admitted and 47 (45.6%) cases were discharged. There is no significant difference between admission rates and these variables: Age, Weight, Height, BMI (Body Mass Index), History of previous hospitalization, Living place (urban/rural), peripheral edema and some spirometric parameters, but significant difference were seen between admission rates and these variables: Functional stage of dyspnea, Pulsus Paradoxus, Intercostal retraction, Respiratory Rate (RR), Heart Rate, Arterial saturation of oxygen, Artieal pH. Variables that predict admission rates in our patients are as follows: Sex, RR and SaO2 in first visit, PEmax in second measurement.

Conclusion: Finding those variables that predict admission in asthmatic patients is very important and cost effective. We recommend further studies in this field especially in measurement of new pulmonary function variables such as PImax and PEmax.

Key words: Asthma, emergency, PEmax

P887
Determining of predicting factors affecting disposition of patients with acute asthma referred to emergency ward
All Taghizadeh, Tabarzidouz and Lung Diseases Research Center, Tabriz, University of Medical Sciences, Tabriz, Islamic Republic of Iran

Introduction: Acute asthma is associated with morbidity and mortality in patient referred to emergency department (ED). Our study was focused on simple objective measures in ED to predicting factors affecting disposition of patients with acute asthma referred to emergency ward.

Methods and materials: Data were collected prospectively at one center over 12-month period on 103 adult patients. Asthma step severity categorization and management was determined by GINA guidelines. Presenting ED vital signs, GSK values, pulmonary function testing (spirometry, flow-volume loop, Pmax, PEmax) and disposition were recorded for each study subject.

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Conclusion: Finding those variables that predict admission in asthmatic patients is very important and cost effective. We recommend further studies in this field especially in measurement of new pulmonary function variables such as PImax and PEmax.

Key words: Asthma, emergency, PEmax

P888
Comparative efficacy of the therapy strategies for the asthma control maintenance in real clinical practice
Evgeny Kulikov, Ludmila Ogurodova, Ivan Deev. Faculty Pediatrics, Siberian State Medical University, Tomsk, Russian Federation

Introduction: Today there is no clear answer to the question which therapy regimen will be optimal for disease control maintenance in real clinical practice. Aim: To compare the efficiency of strategies of control achievement from position of maintenance control in patients with persistent asthma in real clinical practice by ACE-test.

Methods: Multicenter prospective 24-week observation study was conducted in 19 centers in Russia. Investigator was only to record the changes of therapy prescribed by the physician of patient. Patients were aposteroir stratified into three groups: A - step-up regimen of combination therapy (salmeterol/fluticasone propionate), B - stable regime, C - step-down regime.

Result: According to the inclusion criteria the patients in all groups had the uncontrolled disease course (ACE score <20). Of the 288 patients (50%) who achieved control in the first 3 months of observation, 263 (91.3%) persons maintained or increased the disease control level and only 23 (8.0%) of the patients “lost” the disease control. The ACE score decreasing to the uncontrolled level (<20 points) in group A and B was registered in 7.7% and 2.8% of cases, respectively. The significantly biggest proportion of patients with the loss of asthma control was registered in group A and B was registered in 7.7% and 2.8% of cases, respectevely. The highest emergency visit frequency was registered in the group C (18.2%; Group A - 2.6% and B - 5.8% (p<0.001 vs A; p=0.01 vs B).

Conclusion: In the real clinical practice the use of combination therapy at step-up dose or in stable dose are optimal.

P890
Effect of whole body periodic acceleration on airway endothelial function in smokers, non-smokers and asthmatics
Jose Caneco, Elia Mendes, Johana Araña, Patricia Rebollo, Cameron Dezfulian, Adam Wanner. Pulmonary, Critical Care and Sleep Medicine, University of Miami Miller School of Medicine, Miami, FL, United States

Rationale: Cigarette smoking and asthma are associated with attenuated endothelium-dependent vasodilation in the airway. Endothelial shear stress actives endothelial nitric oxide synthase (eNOS), leading to endothelium-dependent vasodilation. It has been shown that whole body periodic acceleration (WBPA), activates eNOS. However, the effect of WBPA on endothelial function in the airway has not been investigated.

Objective: To assess the effect of a single WBPA session on beta-2 agonist induced, endothelium-dependent vasodilation (ΔAQw) in 15 current smokers, 15 never-smokers with asthma, and 15 healthy never-smokers, with the expectation that the treatment would transiently improve endothelial function.

Methods: ΔAQw was defined as the Qw response to inhaled albuterol (180µg). Normal and S-nitrosothiol blood levels (NO) were assayed using a tri-iodide based reductive chemiluminescence method. All measurements were made before and immediately after a 45 minutes WBPA treatment using ExerRest®.

Results: WBPA increased mean baseline Qw by 15.1±4.3±3.5 µl/mmHg in non-smokers (p<0.001) but had no effect on Qw in smokers and asthmatics. ΔAQw remained unchanged in all three groups. NO levels tended to increase in asthmatics (13%) and non-smokers (31%), but the changes did not reach statistical significance.

Conclusions: A single session of WBPA increases airway blood flow in healthy non-smokers, but not in smokers and asthmatics. The treatment has no effect on the blunted endothelium-dependent vasodilation in smokers and asthmatics nor does it augment normal endothelium-dependent vasodilation in healthy non-smokers despite a tendency toward eNOS activation

P891
Successful implementation of an asthma care bundle in a UK hospital
Ali Taghizadieh. Tuberculosis and Lung Diseases Research Center, Tabriz, Iran

Introduction: A care bundle is a checklist of guidelines for clinicians. These have been successfully implemented in areas such as central line sepsis & ventilator-acquired pneumonia. We proposed that a care bundle would improve acute asthma care & outcomes by providing key clinical prompts. The 2009 British Thoracic Society (BTS) asthma audit highlighted areas for improvement, including PEFR and SpO2 documentation, inhaler technique review & use of written action plans. Aims and objectives: To assess the impact of an asthma care bundle on concordance with UK asthma standards.

Method: A checklist sticker was created, piloted & implemented on acute medical wards, and the impact assessed using the 2010 BTS asthma audit.

Results: Pre- and post-care bundle results are shown in Table 1 (care bundle elements shown in bold)

Table 1. Summary of pre-bundle (2009) and post-bundle (2010) BTS audit outcomes

<table>
<thead>
<tr>
<th>Element</th>
<th>2009 (n=32)</th>
<th>2010 (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management on admission</td>
<td>PEFR documented</td>
<td>71.9%</td>
</tr>
<tr>
<td></td>
<td>SpO2 documented</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>ABG documented if SpO2 &lt;92% on air</td>
<td>75.0%</td>
</tr>
<tr>
<td></td>
<td>Hypercapnia on ABG</td>
<td>18.8%</td>
</tr>
<tr>
<td></td>
<td>Systemic steroids within 4 hours of admission</td>
<td>69%</td>
</tr>
<tr>
<td>Impotent management</td>
<td>Inhaler technique review</td>
<td>18.8%</td>
</tr>
<tr>
<td></td>
<td>Discharged on oral corticosteroids</td>
<td>84.3%</td>
</tr>
<tr>
<td></td>
<td>Preventer treatment increased on discharge</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>Discharge PEFR documented</td>
<td>68.8%</td>
</tr>
<tr>
<td></td>
<td>Written action plan</td>
<td>6.3%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Hospital follow-up</td>
<td>71.9%</td>
</tr>
<tr>
<td></td>
<td>Hospital follow-up within 4 weeks</td>
<td>87.0%</td>
</tr>
<tr>
<td></td>
<td>Advice to see GP within 1 week</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Conclusion: Use of the care bundle improved acute asthma care, particularly pre-discharge education & planning. Further work is needed to assess longer-term impact e.g. readmission rates, and the bundle is being revised in light of the latest audit data.
Montelukast plus inhaled budesonide versus double dose inhaled budesonide in nonasthmatic eosinophilic bronchitis
Chang Cai, Shui-Qing Zhong, Yan Yang, Nan-Shan Zhong. Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
Background: Montelukast added to inhaled corticosteroids (ICS) has been demonstrated to relieve asthma symptoms and control airway inflammation equal to double dose ICS. However, the clinical efficacy of montelukast as add-on therapy to ICS has not been reported in nonasthmatic eosinophilic bronchitis (NAEB).
Objectives: Whether add-on therapy with montelukast to inhaled budesonide would equal double dose inhaled budesonide in alleviating cough and airway eosinophilia in adult patients with steroid-naive NAEB was studied, the primary endpoints were changes of cough visual analogue score (CVAS) and eosinophil ratio in induced sputum (EOS) during treatment.
Methods: 26 nonsmoking subjects were randomized to receive either montelukast 10mg qd plus budesonide turbuhaler 200 μg bid (MONT-BUD) or budesonide turbuhaler 400μg qd bid (BUD) for 4 weeks. CVAS, EOS at baseline, 1 week, 2 week and 4 weeks after treatment were measured. Adverse reactions were monitored.
Results: The two groups were comparable in age, median duration of cough and baseline CVAS. Median baseline EOS of MONT-BUD and BUD was 11.8% and 22.7%. Improvement of CVAS was more profound in MONT-BUD. In both groups EOS was normalized in both groups at end of therapy with similar EOS reduction at all time points. Both regimens were well tolerated.
Conclusions: This study demonstrated that the addition of montelukast to inhaled budesonide, and to assess safety, was effective and well tolerated alternative to inhaled budesonide with resolution of airway eosinophilia and more remarkable reduction of cough in NAEB.

Clinical course and outcome of patients with status asthmaticus in a tertiary care centre in Pakistan over the last ten years
Ali Zubairi, Shahid Javed Husain, Zeeshan Waheed. Medical University Karachi, Sindh, Pakistan
Objectives: To describe the clinical course and predictors of poor outcome in patients with status asthmaticus at a tertiary care centre in Pakistan.
Methods: We collected data in patients aged 16 and above with status asthmaticus demographically, co-morbidities, home medications, APACHE II score, use of ventilatory support, and APACHE II score was 9.30 ± 4.39 vs 13.66 ± 2.08, mean PaCO2 was 53.83 ± 23.07 mmHg vs 80.4 ± 15.13 mmHg and arterial pH was 7.33 ± 0.11 vs 7.21 ± 0.09 among survivors and non survivors respectively.
Conclusions: Our study showed that requirement of ventilatory support was associated with prolonged hospital stay. High APACHE II scores, elevated PaCO2, and decreased arterial pH on admission were associated with increased mortality.

Fluticasone/fornterol combined in a single aerosol inhaler vs budesonide/fornterol for the treatment of asthma: A non-inferiority trial
Anna Bodzenta-Lukaszyk1, Roland Bult1, Beatrix Balint1, Mark Lomax2, Kay Spooner2. 1Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; 2Pulmonary Department, Mainz University Hospital, Mainz, Germany; 3Department of Pulmonary Diseases, ConGrey County Municipal Hospital, Destz, Hungary; 4European Medical Science, Mundipharma Research Ltd., Cambridge, United Kingdom; 5European Medical Operations, Mundipharma Research Ltd., Cambridge, United Kingdom
Background: Fluticasone (FLUT) and formoterol (FORM) are widely prescribed for asthmatics. A combination of FLUT/FORM in a single aerosol inhaler (flutiform®) has now been developed. This trial aimed to determine if FLUT/FORM is non-inferior to budesonide/formoterol (BUDFORM, single inhaler) with regards to efficacy, and to assess safety, in adolescents and adults with moderate-to-severe persistent reversible asthma.
Methods: Eligible patients had an FEV1 of >50% to ≤80% for predicted normal value and ≥15% reversibility in FEV1, following salbutamol (up to 400μg qd) 279 patients were randomised to FLUT/FORM 250/10μg b.i.d (n=140) or BUDFORM 400/12μg b.i.d (n=139) in this 12 week, double-blind, 2-arm, parallel-group trial. The primary efficacy measure was change in morning pre-dose FEV1 from baseline to Week 12.
Results: 261 patients completed (FLUTFORM, n=133; BUDFORM, n=128). Both treatment groups showed improvements in morning pre-dose FEV1 from baseline to Week 12. FLUT/FORM was shown to be non-inferior to BUDFORM, because the lower limit of the 95% CI of the treatment difference (FLUTFORM – BUDFORM) was greater than the pre-defined threshold value of -0.2L (95% CI: -0.130, 0.043L). One patient on FLUTFORM discontinued due to AEs (asthma exacerbation: not related) vs 3 patients on BUDFORM (asthma exacerbation, acute sinusitis: not related: asthma exacerbation: possibly related).
Conclusions: Fluticasone/formoterol combination improved morning pre-dose FEV1 over 12 weeks of treatment; demonstrated comparable efficacy to BUDFORM with regards to this key lung function measure of asthma control and had a similar safety profile.

ACHIEVE: Functional effects of long term ICS treatment in controlled asthma
Angelo Petrosanu, Vittoria Conti, Eirini Lemontzi, Irene Minanni, Francesca Oriolo, Viviana D’Alo, Luciana Locorriere, Claudio Terzano. Department of Cardiovascular and Respiratory Sciences, Sapienza University of Rome, Rome, Italy
Background: Goal of asthma management is the “control” of the disease, monitoring symptoms and FEV1 or PEF. However, in controlled asthma the persistence of a long term asymptomatic airway inflammation may lead to an accelerated functional decline.
Aim: To estimate the protective effect of a long term treatment with low dosage of ICS on functional parameters in controlled asthma.
Methods: 98 asthmatic pts with ACT (Asthma Control Test) ≥20, non-smokers were enrolled in a 3 yrs controlled randomized trial. Patients were divided in 2 groups: group A (49) (ICS) receiving a continuous treatment with inhaled beclometasone MDI100mcg twice daily inhaled salbutamol as needed, group B (49) (control) treated with inhaled salbutamol as needed. Step up therapy was performed as recommended by guidelines. Every 3 months, measures of FEV1, FVC, MEF, RV, TLC, FRC, ACT, PEF, (methacoline) were performed. The primary endpoint were: variation of functional parameters, PD20, and ACTscore.
Results: Δ was the difference between time 0 and at 3yrs. Significant difference was reported for RV/LTC: A 30.9 ± 3.2 (A vs B). B 33.7 ± 4.3 (B vs A+2.5); PD20 (mcg): A 123.5 ± 30.1 (A vs B). B 56.7 ± 24.8 ± 30.5 (A vs B); FEV1/FVC at the attainment of PD20: A 64.2% ± 2.9 (A ± 0.4). B 67.6% ± 3.0 (A ± 4.9). No significant differences reported for FEV1 (A 3.94 ± 3.86), FVC (A 2.57, B 2.15), FEV1/FVC (A 74.7%, B 74.9%), MEF25% (A 1.30, B 1.09), ACTscore (A 20.1, B 19.7), side effects (A 8, B 9).
Conclusion: A long term treatment with low dosage of ICS and the reduction of airway responsiveness are bound to a better preservation of the respiratory function in controlled asthma. It is probably due to a better control of a slight air trapping and asymptomatic involvement of small airways, as suggested by the greater decrease of FVC at PD20 in non treated group.

Omalizumab: IgE antibodies may improve remodeling in a mouse model of asthma
Mari Mizuguchi1, Takenori Okada2, Risuko Seki1, Kyoko Ohmori1, Kazunori Fukuda1, Keizichi Akasaka1, Kenya Koyama1, Naoto Fukue1, Hironori Sagara2. 1Dept of Respiratory Medicine, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Saitama, Japan; 2Internal Medicine, Jobu Hospital for Respiratory Disease, Maebashi, Gunma, Japan, 3Koshigaya Hospital Joint Research Center, Dokkyo Medical University, Koshigaya, Saitama, Japan
Recent studies have confirmed that omalizumab, an anti-immunoglobulin E (IgE) antibody, has a high response rate in patients with severe asthma who satisfy conditions such as the use of high-dose inhaled steroids and poor respiratory function. However, the effect of omalizumab on airway remodeling, a characteristic feature of chronic severe asthma, remains to be confirmed. In this study, we compared the effect of omalizumab with that of steroids in a mouse model of remodeling. BALB/c mice were continuously sensitized to ovalbumin to produce a model of remodeling. After the remodeling model was prepared, four groups were studied: an IgE neutralizing antibody group (A), a steroid group (B), an IgE neutralizing antibody plus steroid group (C), and an untreated control group (D). Basement membrane thickening, used as a marker of remodeling, was found to be significantly inhibited in the group A, as compared with the other groups. The group B showed a trend toward inhibition of basement membrane thickening, but the effect was weaker than that in the group A. In the group C, basement membrane thickening was significantly suppressed in a synergistic fashion.
Airway remodeling, a characteristic of chronic severe asthma, was significantly inhibited by treatment with IgE neutralizing antibodies. Concurrent treatment with steroids was markedly effective. On the basis of these results, omalizumab is expected to be therapeutically effective for severe refractory asthma. The finding that treatment with steroids alone was less effective than combined treatment suggested that IgE neutralizing antibodies might also have a steroid-sparing effect.
98. Monitoring exacerbations of airway diseases

P897 Impact of checklist proforma on discharge and follow up care of patients admitted with COPD exacerbations
Mithun Murthy, Rababeh Sarkar, Holly Metcalfe, Sophie Taylor, Gwennan Jones, Jacqueline Bayliss, Robert Stead, Marta Babores. Respiratory Medicine, Macclesfield DGH, East Cheshire NHS Trust, Macclesfield, United Kingdom

COPD management involves a multidisciplinary approach with input from specialist nurses, physiotherapists and dieticians. In 2009, we audited 14 criteria (NICE guidance) and showed scope for improvement. A discharge checklist was introduced.

Aim: To assess impact of discharge proforma on care of patients admitted with COPD exacerbations.

Methods: All COPD patients admitted over Mar-Aug ’09 and Aug-Dec ’10, pre and post introduction of discharge checklist. Data collected: physician and nurse follow up, oxygen assessment, smoking cessation, pulmonary rehabilitation, COPD alert cards, dietetic follow up, domiciliary physiotherapy, community matron follow up, discussion regarding future ventilation, information leaflets, vaccination advice and psychological support.

Results: Table shows comparative results.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>2009, % (No. 58)</th>
<th>2010, % (No. 59)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Physician Follow Up</td>
<td>30</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory Nurse Follow Up</td>
<td>50</td>
<td>90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Referral for Oxygen assessment</td>
<td>24</td>
<td>79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking Cessation referral</td>
<td>50 (No. 20)</td>
<td>80 (No. 10)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary Rehab referral</td>
<td>(6 No. 49)</td>
<td>26 (No. 23)</td>
<td>NS</td>
</tr>
<tr>
<td>COPD Alert Cards issued</td>
<td>2</td>
<td>51</td>
<td>0.00</td>
</tr>
<tr>
<td>Dietetic referral</td>
<td>6</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Domiciliary Physiotherapy referral</td>
<td>12</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Community Matron referral</td>
<td>20</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Discussion regarding future ventilation</td>
<td>0</td>
<td>59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient information leaflet given</td>
<td>4</td>
<td>69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Flu vaccine advised</td>
<td>4</td>
<td>90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pneumococcal vaccine advised</td>
<td>4</td>
<td>90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Psychological support offered</td>
<td>0</td>
<td>90</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: Introduction of a discharge checklist led to significant improvements in referrals to respiratory nurse, oxygen assessment, COPD alert cards, leaflets and vaccination advice. We have continued to use this intervention in our hospital.

P898 COPD assessment test correlation with the increase of the inflammatory markers in COPD exacerbations
Zemo-Ioan Fratila, Ionela Iovan, Dorin Vancea. Pneumology, Clinical Hospital of Infectious Diseases & Pneumology Dr. Victor Babes, Timisoara, Timis, Romania

Introduction: COPD is associated with systemic inflammation and it is a known fact that the COPD exacerbations are accompanied by an augmentation of the serum levels of the inflammatory markers. Aim of the study was to evaluate a correlation between the level of systemic inflammatory markers and COPD Assessment Test (CAT) score in patients with hospitalization COPD exacerbations.

Methods: The CAT test questionnaire was implemented in 53 patients COPD GOLD stage II-IV acute exacerbations. The score changes obtained were compared with the modification of usually serum inflammatory markers (erythrocyte sedimentation rate, CRP, fibrinogen).

Results: It was found that from the group of 53 patients, 14 had a score of >30, 31 had 20-30, 8 between 10-20 and none had a score <10. Meanwhile, the serum inflammatory markers, were significantly altered from their initial value in 2 (41.5%) of the 53 subjects, 10 from the group who had the highest CA test score, 11 from the second group and 1 from the last group.

Conclusions: There is a level of correlation between the high values of serum inflammatory markers and the CA test scores, obvious in patients with moderate to severe exacerbations, presenting a higher CAT score (78.57%) in contrast (p<0.0108) with a weak association (12.5%) in patients with low score of the questionnaire and mild exacerbations.

P899 Detection of acute health status deterioration among COPD patients by monitoring COPD assessment test score
Chaichan Pothirat, Warawut Chairung, Aikhum Limsunan, Atthavut Deesomchok, Chalerm Liewsrisakul, Chaiwat Buranongkit. Div. of Pulmonary, Critical Care and Allergy, Dept. of Internal Medicine, Chiang Mai Univ., Chiang Mai, Thailand

Background: The COPD Assessment Test (CAT) is a valid and simple questionnaire to quantify health status of COPD in routine clinical practice, therefore, it should play a role for detecting acute health status deterioration during monitoring visit.

Objective: To evaluated the discriminative properties of the CAT scores for detecting worsening and exacerbation of COPD patients in Thailand

Methods: The CAT questionnaire was administered to 123 stable COPD patients attended at our chest clinic. These patients were monitored every 1-3 month interval for detecting worsening and exacerbation by using CAT score, physician and patient global assessment.

Results: A total of 237 visits among 123 patients, age 70.9±8.5 years, FEV1=47.3±7.3 ml vs 47.9±18.4% predicted were followed. The mean score change in stable COPD was 0.28 (95%CI=0.06-0.97) and 0.45 (95%CI=0.06-0.97) by patient and physician global assessment. CAT scores were significantly higher at the time of worsening and exacerbation: the mean score changes were 5.97 (95%CI=4.68-7.24) and 9.25 (95%CI=7.10-11.79), respectively. The area under the ROC curve of CAT score for detection of acute health status deterioration was 0.92 (95%CI=0.88-0.96) and the cut-off point score at ≥12 had sensitivity, specificity and accuracy=76.74%, 64.43% and 66.67%, respectively.

Conclusions: The CAT score change during monitoring visits is useful for detecting acute health status deterioration

P900 Use of COPD assessment (CAT) test in monitoring acute exacerbations
Irfan Shafiq, Kayleigh Huggett, Lualat Idris, Ranu Roslan, Timothy Shaw. Thoracic Medicine, Royal Bournemouth Hospital, Bournemouth, United Kingdom

Introduction: The COPD Assessment Test (CAT) is a new patient completed questionnaire that has recently been validated to provide a simple assessment of health status in COPD. It is known that patients with moderate to severe exacerbation score about 5 units higher on CAT [1] and hence it may be useful in diagnosing and monitoring exacerbations.

Methods: We administered the CAT at the time of presentation with exacerbation and at the time of discharge home. We also measured the FEV1 on both encounters.

Results: We have results of 102 patients (60 men and 42 women). The initial mean CAT score was 22.55 and it improved to 19.2 by the time of discharge, this is an improvement of 3.27 points in CAT score on recovery from exacerbation. Although the mean improvement in CAT was not as high as 5 points, the difference between the two Cat scores was highly significant (p=0.002). Mean FEV1 improved from 0.89 to 1L but the difference was not statistically significant (p=0.073). The full results are displayed in the table below:

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Results</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>0.42</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>71.2±10</td>
<td></td>
</tr>
<tr>
<td>Mean CAT on admission</td>
<td>22.55</td>
<td></td>
</tr>
<tr>
<td>Mean CAT on discharge</td>
<td>19.2±10</td>
<td></td>
</tr>
<tr>
<td>Mean FEV1 on admission</td>
<td>0.89 L</td>
<td></td>
</tr>
<tr>
<td>Mean FEV1 on discharge</td>
<td>1.01 L</td>
<td></td>
</tr>
<tr>
<td>Change in mean CAT admission to discharge</td>
<td>3.27 (p=0.002)</td>
<td></td>
</tr>
<tr>
<td>Change in mean FEV1 admission to discharge</td>
<td>0.11 L (p=0.073)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: CAT might be a useful tool in monitoring recovery from COPD exacerbation and could help to determine the optimum time for discharging patient from hospital. Larger studies are needed to validate this use of CAT.


P901 Evaluation of high-sensitivity C-reactive protein in acute asthma
Ebrahim Razii1, Hassan Ehteram2, Hossein Akbari1, Vajjhe Chavoshi1, Armin Razii2, 1Department of Internal Medicine, University of Medical Sciences, Kashan, Islamic Republic of Iran; 2Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Objective: High sensitivity C reactive protein (HS-CRP) is an inflammatory marker known to be related to inflammation, infection, and cardiovascular disease. The aim of this study was to evaluate hs-CRP levels in serum of asthmatics and their relationship to pulmonary function tests, serum IgE levels, peripheral blood white blood cells (WBC) counts.

Methods: The study groups were 108 patients with acute asthma and 93 healthy volunteers. The levels of hs-CRP of 108 patients with acute bronchial asthma and 93 non-asthmatic control subjects were measured. Spirometry, serum immunoglobulin-E (IgE) measurement, WBC and counts were done in all the patients and control groups.

Results: Mean serum hs-CRP levels were significantly higher in patients with acute asthma compared with control (5.47±7.33 mg/l versus 1.46±1.89 mg/l, p<0.001). Among asthmatic patients, mean hs-CRP levels did not correlate with indices of pulmonary function (forced expiratory volume in one second/forced vital capacity and forced mid-expiratory flow), serum IgE level, eosinophil count and WBC.

Conclusions: Increase in serum C-reactive protein levels measured by high-
sensitivity assays may be associated with airflow obstruction in acute asthma, and may be useful as a sensitive marker and a diagnostic tool for detecting and monitoring airway inflammation in patients with acute asthma. In our study of patients with acute asthma, it did not reveal any significant correlation between hsCRP and pulmonary function tests, total serum IgE, and peripheral blood white blood cells counts.

P902 Effects of home oximetry on chronic obstructive pulmonary disease exacerbations Mei Ying Chew, T.K. Lim, Pauline Chong, Min Tang, Charmaine Lim. Department of Medicine, National University Hospital, Singapore, Singapore

Background: A large proportion of patients with chronic obstructive pulmonary disease (COPD) require hospitalized care, often at a very high frequency. 

Aims: We hypothesize that home monitoring with pulse oximetry (SpO2) would enable patients to detect exacerbations and start action plans earlier so as to reduce hospitalizations, and also to improve symptom control and quality of life (QOL) by providing earlier guidance.

Methods: We enrolled COPD patients from a university hospital. They were provided with SpO2 for 6 months and were educated on their use to augment action plans for exacerbations. Home exercise was measured with pedometers. The primary outcomes were hospitalization days, emergency department (ED) attendances and intensive care unit (ICU) days. We also measured QOL and 6 minute walk.

Results: We enrolled 26 patients with mean (SD) age 73 (9) years and mean FEV1 (SD) 47 (17)% pred. There were 84 (6) hospital days vs 50 (2) hospital days (p=0.16) at 6 months. There were 7 (1) ICU days at baseline vs none (p=0.12) at 6 months. The mean SGRQ score was 32 (16) vs 27 (14) at 6 months (p=0.003). The 6 minute walk test (207 (56) vs 212 (67) at 6 months) and pedometer steps (4007 (2706) steps vs 4421 (2969) steps) were also not significantly better. There was 1 death.

Conclusions: In a comprehensive care setting, self-monitoring of SpO2 in patients with severe COPD may have little effect on hospitalizations and quality of life.

P903 Clinical validity of urinary and blood desmosine as biomarkers for chronic obstructive pulmonary disease Jeffrey 6 minute walk test, Ecklas Chaudhuri1, Aly Barton1, Jeffrey Brady1,2,3, Christian Grierson1, Osama Alsahebran1, Petra Rauchaus1, Christopher Weir4, Martina Messow1, Charles McSharry1, Giovanna Feinstein1, Sonntha Mahkophady1, Colin Palmer1, Douglas Miller1, Neil Thompson1, Thomas Sherrington1, Translational Medicine Research Collaboration, University of Dundee, Dundee, United Kingdom; 2Clinical Research, Pfizer Worldwide Research & Development, Collegeville, United States; 3Biomedical Research Institute, University of Dundee, Dundee, United Kingdom; 4Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, United Kingdom; 5Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom

Background: Although the elevation of degraded elastin products in patients with COPD has been reported for many years, its clinical validity and utility remain uncertain due to several difficulties, small study cohorts and unknown relationship between elastin degradation and exacerbation. 

Aims and objectives: To determine the validity of urinary and blood total desmosine/isodesmosine (u/dES) as disease phenotyping biomarkers for COPD and to evaluate their relationship to exacerbation status.

Methods: u/DES and bDES were measured using validated isotopic dilution LC-MS/MS methods.

Results: Two cohorts consisting of a total of 390 subjects including the following groups: healthy volunteers, stable asthma, stable COPD and COPD during an exacerbation.

Conclusions: Our results strongly suggest that bDES is a valid biomarker for phenotyping “accelerated elastin degradation” subtype in COPD whilst uDES links to exacerbation.

Methods: A prospective study of patients, who were evaluated to be included in a Respiratory Rehabilitation (RR) programme, was carried out. We analyzes age, gender, BODE, smoking history, symptoms, comorbidities, quality of life questionnaire (SGRQ). We used The Chronic Respiratory Questionnaire (CRQ) and anxiety-depression (HADS); spirometric values, 6 minutes walking test, maximal effort test, submaximal test, and the number and characteristics of the exacerbations during the previous year. We distinguished 2 groups: Frequent exacerbating patients (>2 exacerbations per year) and non-exacerbating patients (<2).

Results: We included 41 patients: 20 showed >2 exacerbation per year vs 21 showing <2. By comparing both groups, we couldn’t find differences regarding age, gender, smoking history, BMI, symptoms, comorbidities or COPD severity classification (GOLD). There were no significant differences in HADS, although there were some in SGRQ (45.27±18.27 vs 65.76±14.48, p=0.001) and CRQ (91.06±21.78 vs 73.84±21.92, p<0.034). No differences in pulmonary function parameters or tolerance to effort were found. A subgroup (n=5) which, due to their severity could not complete some tests properly, showed no differences when analyzing the different variables, except in SGRQ.

Conclusions: 1. About half of patients who assisted our RR practice were frequent exacerbating patients. 2. Showing more exacerbations does not imply a worse tolerance to effort or a different clinical and functional profile, although it affects directly their quality of life.

Background: CF is characterized by progressive BE and small airways disease. 

BE is related to the number of exacerbations and Health Related Quality of Life (HRQoL), assessed by the Cystic Fibrosis Questionnaire-Revised (CFQ-R). 

Objective: 1) Investigate predictive value of BE score and CFQ-R respiratory domain score (CFQ-R resp) for exacerbations. 2) Determine added predictive value of CFQ-R resp on top of BE score to predict number of exacerbations in the year following. 

Methods: Cohort study (July 2007 to Jan 2010) in clinical stable children and adolescents with CF, whom had routine chest CT and CFQ-R as part of their (bi)annual examination. CT scans were anonymized and randomly scored using CFCT BE score, expressing BE as % of maximum score. CFQ-R was completed by children aged 6-13 years and their parents or by adolescents aged ≥14 years.

Conclusion: BE and HRQoL have potentialities to predict the number of exacerbations in CF. A point increase on the CFQ-R resp results in a 6% reduction of the number of exacerbations.

P906 Factors determining duration of hospital stay in patients hospitalized for acute COPD exacerbation Filia Diamantea, Stamatina Tsiskria, Fotini Karakontaki, Dimitrios Mitromaras, Elef Stagaki, Emmanouil Kostanakis, Vlasis Polychronopoulos. 3rd Respiratory Medicine Department, Samosogeleon General Hospital, Athens, Greece

Background: Factors associated with the length of hospitalization in patients admitted for acute exacerbation of COPD (AECOPD) have not been thoroughly evaluated.

Objectives: To evaluate the association between clinical and functional parameters and duration of hospital stay of patients admitted due to AECOPD.

Methods: We studied prospectively 31 patients (20 men, 11 women), mean age 69.5 (±7.8) years, admitted to hospital for AECOPD. Pulmonary function tests including body box evaluation of lung volumes, Borg dyspnea score at rest, Visual analogue scale dyspnea score, 6 minute walking test (6 MWT), Chronic Respiratory Questionnaire (CRQ) total and 4 domains scores, Charlson index for comorbidities, blood gases on admission, were all parameters evaluated within 72h of admission. Frequency of exacerbations, long term oxygen therapy (LTOT) prior to admission and duration of hospital stay were also recorded.

Results: Mean duration of hospital stay was 8 days. Patients divided in 2 groups: group 1 (18 patients): duration of stay < 8 days, group 2 (13 patients): duration of stay ≥ 8 days. Patients in group 2 had lower FEV1% pred [34 (27, 39)] vs 48

SUNDAY, SEPTEMBER 25TH 2011 155s

Furnaceutic SpA, Visit Chiesi Farmaceutici SpA, at Stand D.30
Diagnosis in patients with PcCO₂ < 25 mmHg

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Mean PcCO₂ (mmHg)</th>
<th>Mean PaCO₂ (mmHg)</th>
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</thead>
<tbody>
<tr>
<td>COPD</td>
<td>7</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>4</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>OSA</td>
<td>2</td>
<td>58.1</td>
<td></td>
</tr>
<tr>
<td>Overlap Syndrome (COPD+OSA)</td>
<td>2</td>
<td>54.7</td>
<td></td>
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<tr>
<td>IPF</td>
<td>2</td>
<td>55.1</td>
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<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Dyspnea under evaluation</td>
<td>2</td>
<td>33</td>
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SD of PcCO₂ in PaCO₂ < 25 mmHg

<table>
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<th>N</th>
<th>Mean PcCO₂ (mmHg)</th>
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SD of PaCO₂ in PaCO₂ < 25 mmHg

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<td>Dyspnea under evaluation</td>
<td>2</td>
<td>33</td>
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</tbody>
</table>

Conclusion: VentCheck analysis is feasible & has potential role for spot analysis of ventilation in outpatient or inpatient setting in non invasive manner without any complications.

P908 Early detection of asthma exacerbations and the use of action points for treatment decisions in self-management plans

Peter J. Hommao1, 2, D. Robijn Taylor1, Jiska B. Snoek-Strobos1, Jacob K. Sent1. 1Department of Medical Decision Making, Leiden University Medical Center, Leiden, Netherlands; 2Department of Medicine, Academic Medical Center, Amsterdam, Netherlands

Background: Written asthma action plans specify the level of symptoms or peak expiratory flow (PEF) (action points) at which to increase medication in order to prevent or reduce severity of exacerbations. Few currently used action points are validated. Our aim was to develop optimal action points for early detection of asthma exacerbations.

Methods: We analyzed daily morning PEF and symptoms from two studies. The development dataset consisted of 165 patients and 88 exacerbations (Taylor, Thorax 1998). Every week was coded “stable week” or “pre-exacerbation week”. Potential action points were based on Quality Control Analysis of PEF or symptoms, or percentage personal best. Sensitivity and specificity for predicting an exacerbation and the number of days the exacerbation was diagnosed earlier were calculated. Optimal action points were based on these parameters. Their performance was compared to the published NAEPP action point in the validation dataset, consisting of 94 patients and 20 exacerbations (Smith, NEJM 2005).

Results: The main differences between action points were in false positive rate and early detection (Table 1). Combination of PEF+symptoms action points performed best, due to improved specificity and early detection.

Conclusion: Early detection of asthma exacerbations can be improved by combining symptoms and peak flow measurements over one week in a single action point.

P909 Regular follow-up in severe asthma may reduce the rate of exacerbations and the FEV₁ decline

Federico L. Dente, Federica Novelli, Maria Laura Bartoli, Monica Carli, Silvana Cianchetti, Antonella Di Franco, Elena Bacci, Pier Luigi Paggiaro. Cardio-Thoracic Department, Respiratory Pathophysiology Section, Pisa, Italy

Thirtythree subjects with severe asthma (ATS Workshop 2000) were examined over a FU period. Two groups were obtained depending on the adherence to the proposed FU: 21 subjects (8 males, age 63±6.8 yrs, duration of disease 19.6±10.4 yrs) complied with regular follow-up every 3-4 months to measure FEV₁, hypertonic saline induced sputum (group A), while 12 subjects (1 male, age 59.8±6.2 yrs, duration of asthma 21.2±14.8 yrs) performed on demand visits (group B). At each visit, physician could modify the pharmacologic treatment according to symptoms and other measures (functional findings, sputum eosinophilia). No differences among the 2 groups were observed both at baseline and at the end of follow-up, for FEV₁ and sputum eosinophilia and neutrophilia. A decrease in the rate of exacerbations and oral steroid cycles between baseline and the end of FU was found in the group A only. A significantly greater decline in FEV₁ over the FU was observed in the group B with respect to group A.

In conclusion, a regular FU with treatment adjustment obtains a greater control of asthma in terms of exacerbations and oral steroid cycles, and also of long-term FEV₁ decline.

P910 Correlation of dyspnea and physiological impairment in COPD exacerbation

Tijana Cok, Branislava Milenikovic, Predrag Rebic. Clinical Department, Clinic for Pulmonary Diseases, Clinical Centre of Srbia, Belgrade, Serbia

Dyspnea is a primary symptom of COPD. The Medical Research Council (MRC) scale, Baseline Dyspnea Index (BDI), Visual Analogue Scale (VAS) and Borg scale are widely used for evaluation of limitation of activities due to dyspnea in patients with COPD. There is limited information on how these scales relate with parameters of physiological impairment. To aim of the prospective study was to analyze the correlation between MRC, BDI, VAS and Borg dyspnea scales and multiple measures of physiological impairments in COPD exacerbation. Forty five patients (age 62.7±9.9 with COPD exacerbation (GOLD stages III and mostly IV) were analyzed at admission to the hospital. Physiological impairments were assessed by spirometry (FVC, FEV₁), body plethysmography (TLC, RV, FRC, IC), respiratory muscle strength (Pimax), arterial blood gas analysis (ABG) and 6-min walking distance (6MWD).

The correlation between MRC scale and FEV₁ is r = -0.427 (p < 0.05), FVC is r = -0.420 (p < 0.05), Pimax is r = -0.601 (p < 0.01). The correlation between BDI and FEV₁ is r = 0.493 (p < 0.01), Pimax is r = 0.613 (p < 0.01), 6MWD is r = 0.569 (p < 0.05). The correlation between Borg scale and FEV₁ is r = 0.521 (p < 0.01), FVC is r = -0.408 (p < 0.05). Pimax is r = -0.462 (p < 0.05). TLC is r = 0.483 (p < 0.01), RV is r = 0.410 (p < 0.05), FRC is r = 0.443 (p < 0.05). VAS has correlated with FEV₁ (r = -0.385, p < 0.05), Pimax (r = -0.464, p < 0.05) and 6MWD (r = -0.536, p < 0.05). The correlation between dyspnea scales and BDI was not significant. In our study all dyspnea scales have correlated with FEV₁ and Pimax. According to our results it could be concluded that Borg scale is a good tool for assessing dyspnea during exercise and the therapeutic response in COPD exacerbation.
99. Monitoring with lung function tests in airway diseases

P91 Pulmonary function in sarcoidosis: A review of 85 cases using percentage predicted and lower limit of normal values to determine pattern of pulmonary function deficit

Christopher Atkins, Andrew Wilkes, Orizon Twemtany. Department of Respiratory Medicine, Norfolk and Norwich University Hospital, Norwich, Norfolk, United Kingdom.

Previous studies have shown airflow limitation is common in Sarcoidosis. Recent evidence (Chest 2011; 139:52-59) suggests using fixed percentage predicted (PP) values may discordantly classify patients compared to using fifth percentiles as the lower limit of normal (LLN). We studied PFT patterns, and the effect of classifying by PP and LLN.

Our study assessed the PFT results found in consecutive patients presenting with Sarcoidosis to one medical team over a 14-year period. Eighty-five patients fulfilled the entry criteria. All had FPTs available. Patients were classified into normal, obstructive, restrictive and mixed deficits using the ATS/ERS flowchart for PFT interpretation. Classification by PP and LLN values were compared. Eleven patients (12.9%) were classified discordantly comparing PP with LLN. There were six normal PFTs classified by LLN, but abnormal by PP values. Normal lung function (PP 64.7%, LLN 68.2%) was the commonest pattern. Obstruction was the commonest abnormality (PP 24.7%, LLN 21.7%). Patients with obstructive deficits were more likely to have ever smoked.

The frequency of airflow obstruction in this study was 24.7% when classified by PP, equivalent to findings from a similar cohort (Resp Med 1991; 59-64 - 24.3%)

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P911 Serum uric acid and uric acid/creatinine ratio in exacerbations of COPD

Alexis Papadopoulos1, Konstantinos Burzilda2, Akaiten Hamiotou1, Konstantinos Kostikas1 2 Respiratory Medicine Department, Amalia Fleming Hospital, Athens, Attiki, Greece; 2 2nd Respiratory Medicine Department, University of Athens Medical School, Athens, Attiki, Greece.

Background: Tissue hypoxia triggers the degradation of purine and Uric Acid (UA) is an end product of this metabolic pathway, and therefore may reflect the severity of hypoxia. Only a few studies have focused on the role of uric acid in patients hospitalized for exacerbations of COPD (ECOPD).

Objectives: To evaluate the associations of UA and Uric Acid/Creatinine ratio (UA/Cr) with clinical parameters related to disease severity for patients hospitalized for ECOPD.

Methods: UA and UA/Cr and parameters related to the severity of ECOPD, including PaO2/FiO2 ratio, MRC dyspnea scale, and Saint George’s Respiratory Questionnaire (SGRQ) were measured on admission. Patients underwent spirometry and 6-minute walking test (6MWT) on stable condition and were followed up for 1 year.

Results: We included 153 consecutive patients (52.8% male; mean age 71.7 years). UA levels were higher in more severe disease according to GOLD stages (6.38 ± 9.1 vs. 6.59 ± 6 vs. 7.45 ± 6 ± 8 vs. 8.90 ± 12 mg/dL respectively; p < 0.001). With similar classification of UA/ Cr levels (p < 0.001). On admission, UA presented significant correlations with PaO2/FiO2 (r=0.16, p=0.44), MRC (r=0.63, p=0.001) and SGRQ total score (r=0.485, p=0.001). UA/ Cr presented similar associations. Baseline levels of UA and UA/ Cr presented significant negative correlations with 6MWD (r=-0.756 and r=-0.734, p < 0.001) and all SGRQ domains on stable condition. Patients in the higher quartiles of UA and UA/ Cr presented more ECOPD and hospitalizations in the year of follow-up, but did not present differences in mortality.

Conclusions: UA and UA/ Cr levels present significant correlations with important expressing COPD severity both on exacerbation and on stable condition.

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P912 Patient experiences of exacerbations in a real world setting: Global results from the Hidden Depths survey

Neil Barnes1, Peter M.A. Calverley 2, Alan Kaplan 3, Klaus F. Rabe4. from the Hidden Depths survey.

P912 variables expressing COPD severity both on exacerbation and on stable condition. hospitalizations in the year of follow-up, but did not present differences in mortality.

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Conclusions: UA and UA/ Cr levels present significant correlations with important expressing COPD severity both on exacerbation and on stable condition.

P913 Impact of climate change on COPD in Berlin-Brandenburg – Developing a telemonitoring based approach for early intervention

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Climate change affects human health. Especially patients with chronic lung diseases seem to be more influenced. Extreme weather, e.g. heat waves, leads to an increase of COPD exacerbations and hospital admissions. In this context a prospective investigation of risks due to climate change for moderate/severe COPD is required, which allow us to determine susceptible subgroups and the development of an early intervention system to prevent exacerbations.

Therefore we designed a combined clinical research module, based on telemonitoring of COPD patients and complex analyses of scaled regional atmospheric conditions (i.e. temperature, humidity, particulate matter) of the metropolitan area Berlin-Brandenburg. We implemented the validated BODE-Index into a telemonitoring system, including home spirometry, a Mobile Medical Assistant (MMA) for self-evaluation and a triaxial pedometer for the quantification of physical activity. This randomized clinical trial contains a cohort of 320 COPD patients, divided into a control group (visit every 3 month) and an intervention group (daily telemonitoring).

The implementation of the telemonitoring system for COPD has been started as proof of concept. Patient compliance is excellent and the system is well accepted. Concluding our results, this new approach for measuring the impact of climate change could lead to new interventional strategies and improve prognosis and quality of life in COPD. Nevertheless, further clinical research concerning the impact of climate change is strongly needed to improve the adaptive response in vulnerable patients with COPD.

*The study is funded by the BMBF (Federal Ministry of Education and Research).
Introduction: The airway reversibility test (ART) is performed to diagnose obstructive airway disease (OAD) such as asthma and COPD. The ART revealed negative result in some asthma patients. It can be made insufficient treatment (Tx) for those patients.

Objectives: We reviewed the patients’ data to evaluate the characteristics of the patients who have marked improvement of spirometry (SPM) after regular Tx among patients with SPM below COPD stage II by GOLD guideline.

Method: We reviewed SPM records of 1072 patients who performed ART to evaluate dyspnea from 1st September 2009 to 30th August 2010. Finally we reviewed the pre and post-Tx SPM data and characteristics of 121 patients who have pre-bronchodilator (BD) FEV1/FVC <70%, FEV1 <80%, and negative for ART.

Results: Twenty four patients (19.8%) showed improved FEV1 >80% after regular Tx with ICS and/or tiotropium (group 1). FEV1/FVC >70% and FEV1 >80% (group 2). The mean increment of FEV1 are 0.47 L and 0.61 L in group 1 and 2. The increment of FEV1 after Tx slightly correlated with initial post-BD FEV1 change in ART (r=0.23, p=0.019). But, the post-BD FEV1 change (%) was not different between group 1 and non-responder group (5.29±4.35 vs 6.71±4.51, p = 0.33).

Conclusion: The results of this study about 20% of patients with SPM fitted in moderate COPD had improvement of FEV1/FVC >70% and presence of at least one respiratory symptom (Group C). The prevalence of OAD was 8.9%, <4.8%; p=0.01) and SAO (Δ 4.8%; p=0.01) and SAO (Δ 21.5%; p<0.0001) than presence of respiratory symptoms. We recommend use of PFM as a screening tool for OAD in large epidemiological studies.

Introduction: CF lung disease starts in small airways. SAD is visible on chest-CT as trapped air (TA). For routine monitoring of CF lung disease spirometry parameters are used. Forced expiratory flow after 75% of vital capacity is exhausted (FEF75%) is a sensitive marker of SAD. Lung Clearance Index (LCI) obtained by Single Breath Washout test (MBW) has been advocated as a parameter to monitor SAD. Whether LCI is more sensitive than FEF75 to detect SAD is unknown.

Aim: To study the relation between FEF75 and LCI and trapped air on CT and between FEF75 and LCI.

Methods: Retrospective study of stable CF patients (n=50) who had their (bi)-annual check-up including chest-CT and spirometry. Tidal breathing MBW (n=23) was performed using the Ecomedics Exhalyzer D. In- and expiratory (volumetric) chest-CT scans were scored using the CF-CT score and expressed as% of maximum volume. FEV1, FVC, FEV1/FVC, FEF25-75%, FEF75, FEF200, RV, TLC, R20Hz, and FEF25-75% as% of predicted values.

Results: CF patients (1-19 yrs, male =26). 36% had chronic pseudomonas. FEF75 mean 45.5 (range 7.5-119.2)%, predicted LCI 9.4 (6.9-14.3), TA 33.0 (0.8-3.3)%. FEF75 correlated with LCI (N=23) (r=0.573, p=0.005). FEF75 ± FEV1/FVC correlated with pre-bronchodilator (%FEV1 ± FEV1/FVC) and RV (r=0.520, p=0.001), mucusclogging (r=0.505, p=0.001) parenchymal abnormalities (r=0.508, p=0.001) and total CF-CT score (r=0.535, p<0.001) but not with TA. LCI did not correlate with abnormalities on CT.

Conclusion: FEF75 correlates with LCI. Neither FEF75 nor LCI correlate with TA. The additional value of LCI over FEF75 as a sensitive monitoring tool for SAD requires further validation.

Introduction: The use of forced oscillation technique (FOT) in assessment and stratification of disease severity in elderly COPD patients remains unclear.

Aim: To compare lung function profiles between subjects with BS-COPD and TS-COPD.

Methods: 17 BS-COPD (mean 43 yrs exposure) and 35 TS-COPD (mean 43 smoking pack yrs) underwent pre and post-bronchodilator spirometry to measure FEV1, FVC and FEF25-75%, bodyplethysmography to measure residual volume (RV) and total lung capacity (TLC), impulse oscillometry (IOS) to measure R50H and R20Hz and single-breath DLCO to measure lung diffusion. Two sample “t” test was used to compare mean (%SD) lung function parameters between the two groups.

Results: There were no significant differences in% predicted values for FEV1, FVC, R20Hz, RV and TLC between TS-COPD and BS-COPD (all p values ≥0.05). However, BS-COPD showed a trend towards greater small airway obstruction indicated by lower FEF25-75% predicted values (BS: 9% ±3% vs TS: 12% ±5%, p=0.02), higher R50H predicted values (BS: 272% ±65% vs TS: 222% ±46%, p=0.05) and higher R50H values normalized to total airway resistance [BS: 0.53 ±(0.07) vs TS: 0.46 ±(0.13) p=0.05] while TS-COPD showed lower% predicted values for DLCO [TS: 53% ±24% vs BS: 71% ±33%; p=0.03].

Conclusion: BS-COPD shows similar decrements in Spirometric, IOS and bodyplethysmographic parameters as TS-COPD. However, BS-COPD was associated with greater small airways obstruction, while TS-COPD was associated with lower DLCO values.
Results: Totally, 102 COPD patients with a mean age of 70.3±8.2 and median GOLD stage of 2 were recruited. FOT parameters correlated well with GOLD stages. Among the FOT parameters, FRes was the best to predict disease severity. Cut-off value of FRes >29 has a sensitivity of 71% and specificity 69% in identifying severe patients (%FEV1<50%), with area under curve value 0.77.

Conclusion: FOT is accurate for assessing disease severity in elderly COPD patients. FRes value >29 has a good sensitivity and specificity in identifying severe COPD patients.

P921 Reproducibility data of breath analysis through a gas sensors array and comparison to spirometry in COPD patients
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Background: There is insufficient information on reproducibility and intra-observer variability of breath analysis, a technique proved to have classificatory and discriminative properties in respiratory diseases. Aim of this study is therefore to compare variability over time of breath analysis and global spirometry in elderly patients with COPD.

Materials and methods: Data refer to the 9 COPD patients so far recruited. Patient underwent breath analysis and respiratory function study 3 times along a period of 3 weeks. The gas sensors array (based on 6 Quartz Microbalances (QMB) covered with different metalloporphyrins) used for this study was fabricated at Tor Vergata University, Rome. The reproducibility of sensors measurements and spirometry data were then compared.

Results: Results are summarized in figure 1 with panels A, B and C respectively representing the frequency shifts registered by the six QMB sensors (A) and twelve parameters obtained by global spirometry (B and C). Variance, mean value, confidence interval and outliers of a set of data are graphically depicted.

Figure 1

Conclusions: Spirometric values show a smaller variance respect to the QMB frequency shifts. However, the reproducibility of selected sensor data seems fair enough to allow follow up COPD patients.

P922 Patients with fluctuant peak expiratory flow value in the absent category are insensitive to dyspnea and are at risk for severe asthma exacerbation
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Exacerbation of asthma has a negative impact on quality of life and increases the risk of fatal asthma. One of the known risk factors of patients with a history of near-fatal asthma is experiencing mild asthmatic symptoms as opposed to airway obstruction. We set out to find patients carrying such a risk before they experience severe exacerbation of asthma.

To determine the character of such patients, we compared the background and asthma diaries (mean period, 274 days) of 53 asthma patients with their symptoms and peak expiratory flow value (PEF). According to the criteria of the Japanese Society of Allergology, symptoms were classified into 8 categories ranging in severity from absent to severe attack.

Average PEF was 75.2% (50.5–100) in absent, 64.5% (36.6–92.6) in wheeze, 57.3% (25.0–94.7) in mild attack and 43.6% (20.4–83.1) in moderate attack, and the personal best was 100%. Thus, differences in decreased PEF in cases with the same symptoms varied widely between patients. PEF in wheeze, mild and moderate attack did not correlate significantly with the duration of asthma, FEV1 or the proportion of personal best to standard PEF. These PEFs did not show a significant difference in the groups that were divided by regular treatment of asthma, but did show a significant negative correlation with the coefficient of variation of PEF when asthma was absent.

To reveal patients who are insensitive to dyspnea, the most important factor to consider is the coefficient of variation of PEF when asthma is absent. When we find such patients who exhibit fluctuant PEF, we have to intervene in their treatment, even when they claim to be stable.

P923 The use of forced oscillation technique (FOT) in assessment of airway obstruction and airtrapping in elderly COPD patients
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Introduction: Forced oscillation technique (FOT) is a new lung function measurement technique that may have a role in assessing elderly COPD patients.

Aim: To evaluate the accuracy of FOT in assessment of airway obstruction and airtrapping in elderly COPD patients.

Methods: Stable spirometry-confirmed elderly COPD subjects were recruited from Kwong Wah Hospital, Hong Kong, from Jan 10 to Jan 11.

Subjects were assessed by both conventional plethysmography and FOT machine in the same visit. Airway obstruction was measured by FEV1%, Raw, Gaw while degree of airtrapping was measured by residual volume (RV), total lung capacity (TLC), inspiratory capacity (IC) and RV/TLC ratio. FOT parameters like frequency resonance (FRes), frequency dependence (FDep), resistance at 6Hz (R6Hz), average resistance (RAM), average reactance (XAM) were obtained. The FOT parameters were then compared with the plethysmography.

Results: Totally, 106 patients were recruited. 93.1% were male with a mean age of 70.6±8.3 and FEV1 of 54.3±21.3. FOT correlates well with conventional plethysmography for measurement of airway resistance and airtrapping in elderly COPD patients. Among the FOT parameters, FRes showed the best correlation with FEV1 (r=0.608, p<0.001) and RV/TLC ratio (r=0.563, p<0.001).

Conclusion: FOT is an accurate and convenient technique for assessment of airway obstruction and airtrapping in elderly COPD patients.
Aim: To determine ERT long-term effects on pulmonary function and exercise tolerance in late-onset GSDII.

Methods: 7 children (mean age at starting ERT 11 years, 4M:3F) receiving bi-weekly infusion of 86GAA for at least 36 months were evaluated performing pulmonary function tests and 6-min walking tests (6MWT), before (T0) and during treatment (T12, T24, T36).

Results: Our data describe a predominantly restrictive pattern of lung function at baseline, with a significant improvement after ERT.

The 6MWT improved during ERT; analysis of individual performances showed a progressive increase in walking capacity in all the patients. The difference in 6MWT rank distribution at baseline, T12, T24 and T36 was statistically significant (p< 0.05, according to Friedman).

Conclusion: Our data highlight as motor and respiratory functions respond differently to ERT: motor function seems to improve due to an increased peripheral muscular endurance, while pulmonary function remains unchanged after starting treatment. Long-term ERT is effective in improving motor function and in stabilizing respiratory function in late-onset GSDII.

P925 Expiratory flow limitation (EFL) detected non-invasively as a phenotypic character of COPD

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Within-breadth change in reactance at 5Hz during tidal breathing reliably detects EFL in patients with COPD. We used the method proposed by Dellaca et al to determine presence of EFL and its relationship to spirometry and demographics of 424 healthy smokers and COPD patients from the Bergen cohort of the ECLIPSE study.

Aim: Establish the prevalence of EFL by GOLD stage and its relationship to dyspnoea and BMI.

In 274 stable COPD patients and 150 healthy smokers controls performed spirometry and tidal impulse oscillometry.

Results: Presence of EFL in healthy smokers, COPD grade 2,3, and 4 was 7%, 13%, 28% and 40% respectively. Inspiratory resistance and reactance at 5Hz were higher in COPD than smokers but differed little across GOLD stages.

Demographics n BMI MRC FEV1 R5insp X5insp

Healthy smokers non-EFL 149 26.4±4 0.12±0.4 30.4±7.1L 0.26±0.07 >0.09±0.03

EFL 1 32 1.9 ±2.0 3.9L 0.39 ±0.08

COPD GOLD 2 non-EFL 125 26.5±6 1.31±1.0 1.8±0.5L 0.39±0.12 >0.15±0.06

EFL 19 30.6±7 1.91±1.2 1.5±0.3L 0.51±0.06 >0.20±0.05

COPD GOLD 3 non-EFL 76 24±6 1.5±0.9 1.2±0.3L 0.41±0.10 >0.20±0.07

EFL 29 30±6 2.31±1.2 1.1±0.3L 0.50±0.12 >0.22±0.07

COPD GOLD 4 non-EFL 15 22±5 2.61±1.5 0.8±0.2L 0.42±0.10 >0.22±0.10

EFL 10 25±6 2.41±1.4 0.7±0.1L 0.43±0.06 >0.23±0.08

MRC: Medical Research Council dyspnoea scale; R5insp: Inspiratory resistance at 5Hz; X5insp: Inspiratory reactance at 5Hz; *p<0.05.

Conclusion: EFL became more common in higher GOLD stages, but a significant number of patients in all GOLD stages were not flow limited at rest. In GOLD stage 2 and 3 EFL patients were more breathless, despite similar spirometry, but EFL also tracked obesity, which may contribute to both EFL and dyspnoea. Presence of EFL has potential to be an independent phenotypic characteristic in stable COPD.

P926 Area under the maximum expiratory flow-volume curve a sensitive parameter in the evaluation of airway obstruction

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Introduction: The most frequently used parameters for assessing bronchoconstriction and bronchodilatation are forced expiratory volume in 1 s (FEV1) and peak expiratory flow (PEF).

Objectives: To assess the sensitivity of other parameters after induced bronchoconstriction and bronchodilatation.

Methods: Forced vital capacity, FEV1, PEF, maximum expiratory flows (MEF) at 25, 50 and 75% of vital capacity and the area under the maximal expiratory flow-volume (MEFV) curve (Area ex) were measured in two groups of asthmatic patients after induced bronchoconstriction and bronchodilatation.

Results: In 158 asthmatics without airway obstruction, bronchoconstriction was induced by inhalation of 1% histamine aerosol. The 20% fall in Area ex compared to baseline was found in all asthmatics, while the 20 and 15% falls in FEV1 were noted in 31 and 69% of the patients, respectively. Other parameters were less sensitive. Another 102 asthmatics with mild-moderate airway obstruction were treated with various bronchodilators. The 20% increase in Area ex was observed in all asthmatics, while the 20% increase in FEV1 was found in only 28% of the patients and the 15% increase in FEV1 in 56%.

Conclusion: In evaluation of correlation between dynamic functional parameters the most accurate parameter in Areaex – value defining surface under the expiratory part of “flow – volume” curve. Area ex was a sensitive parameter in the evaluation of airway capacity in comparison with MEF1,2, MEF2,5, MEF4, FEF2,5, FEV1 and other parameters measured from the MEFV curve in our study patients.

P927 Determination of predominant site of airway obstruction in patients of bronchial asthma: Role of impulse oscillometry

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Background: The major site of airflow limitation in bronchial asthma varied from central to peripheral airways.

Aims and objectives: To determine predominant site of airway obstruction in patients of bronchial asthma by impulse oscillometry and flow volume loop.

Methods: Twenty five patients of asthma underwent both impulse oscillometry and flow volume loop studies. Predominant site of airway obstruction was determined by impedance spectra and visual lung model of IOS, and parameters of flow volume loop.

Results: Two patients were excluded from final analysis as their impedance spectra showed significant upper airway influence which would have made localization of site of airway obstruction invalid.

Conclusion: In 158 asthmatics without airflow obstruction, bronchoconstriction was shown to be a specific feature of asthma, though this is still a controversial issue. We aimed to evaluate whether variability over time scales >1 day can reliably separate asthmatic from healthy subjects.

Within-breadth respiratory resistance (Rrs) and reactance (Xrs) were measured by forced oscillations during 2min of tidal breathing at morning and evening for 6 months in 10 mild asthmatic and 10 healthy subjects. Short-term (within measurements) and long-term (2, 4, 8, 16 and 32 consecutive days) variability of Rrs and Xrs was characterized by their standard deviations (SDRrs and SDXrs).

Short-term variability of either Rrs or Xrs was not significantly different between asthmatic and healthy subjects (p<0.05). SDRrs was significantly larger in asthmatics than in healthy subjects with a time scale ≤4 days using morning
P929
Determination of respiratory flow by tracheal sound-frequency-analysis
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The established methods to detect the flow are pneumotachographic measurements, which are not always ideal to use regarding long term measurements and measurements during sleep. Thus it is interesting to find an alternative non-invasive method to detect the quantitative value of the flow.

There are some further appendages that use tracheal respiratory sound intensity, but there is no method suitable for measurements during a noninvasive ventilation. The aim was to create a new method, easy to use under different long term conditions, based on tracheal sound-frequency-analysis.

Up to now, 43 subjects (male, non-smoker, normal BMI, 18-60 years old, FEV1>80%) were tested. The subjects breathed during 15 minutes without and with different masks. The measuring method included a respiratory sound sensor which was affixed paralaryngeally on jugular and a pneumotachograph. The flow-curve was calculated using the envelope of frequency spectra via fast Fourier transformation.

It was possible to achieve a very good correlation between the calculated flow-curve and the real flow (R=0.8) in all conditions.

This method is very easy to use and could be established for patients who are not eligible for conventional measurements (infants, measurement during sleep and for patients with noninvasive ventilation).

P930
Peripheral airway function in COPD assessed by Sacin and Scond using SF6 and He multiple breath washout
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Background: Peripheral airways, particularly acinar airways, are involved in COPD. Sacin for SF6 reflects ventilation inhomogeneity deep inside the acinus, while Sacin for He reflects inhomogeneity proximally in the acinus, and Scond indicates inhomogeneity in the small conducting airways. We tested the hypothesis that Sacin and Scond are greater for SF6 vs. He in COPD.

Methods: Multiple breath SF6 and He washout, using a mass spectrometer, was performed at baseline and post bronchodilator (BD, 400 mcg salbutamol and 80 mcg ipratropium pMDI) prior to spirometry and DLCO: 41 COPD subjects (17M/24F), 45-66 yrs, smoking history 10-75 pack yrs. Reference values for Sacin and Scond were obtained in 46 non-smoking healthy subjects aged 19-71 yrs. Local spirometry and DLCO reference equations were used [1,2]. Results were expressed as median (range) z-scores, and wilcoxon rank sum test used for paired comparisons.

Results: SF6 Sacin and Scond z-scores were greater than He indices both at baseline and post BD in COPD subjects (p<0.001 for all).

Conclusions: COPD was characterized by greater ventilation inhomogeneity in the distal vs. the proximal acinar portion. The degree of ventilation inhomogeneity found in COPD within the acinus is greater than in the conducting airway zone.

References:

P931
Spatial heterogeneity in regional pulmonary function in COPD patients and healthy young and elderly subjects
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Introduction: Electrical impedance tomography (EIT) can determine regional dynamic gas volume changes in the lungs. The aim of our study was to examine the regional differences in lung function in COPD patients and healthy adults using EIT.

Patients and methods: 33 COPD patients (GOLD II-IV) and 25 healthy young and elderly adults were studied. EIT data were collected at up to 44 images (Goe-MF II, CareFusion, Hoechberg, Germany) in parallel with spirometry. Regional inspiratory (IVC) and forced vital capacities (FVC), forced expired volume in 1s (FEV1) and tidal volume (Vt) were determined in 912 EIT image pixels in the chest cross-section. Coefficient of variation (CV) was calculated from all pixel values to characterize the heterogeneity of lung function. The average value reflecting the volumetric changes in the cross-section was also determined. Statistical analysis was carried out by one-way ANOVA with Bonferroni post test.

Results: The CV values of regional IVC, FVC, FEV1 and Vt were significantly different between healthy adults and COPD patients (p values: 0.0102, 0.0050, 0.0022 and 0.0047). No differences existed between the young and elderly subjects. The average IVC, FVC, FEV1 and Vt in the chest cross-section were significantly different among the groups (p values:<0.001, <0.001, <0.001 and 0.0054). The highest values were noted in the young subjects, significant differences between the elderly and COPD patients were found for IVC, FVC and FEV1.

Conclusion: EIT is able to detect disease and age related differences in regional lung function. The heterogeneity of lung function is similar in the young and elderly healthy subjects but lower than in COPD patients.

P932
Evaluation of respiratory impedance in COPD by forced oscillation technique using a MostGraph
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Background: COPD is characterized by not fully reversible airflow limitation and defined with the decrease in FEV1 by spirometry. The Forced Oscillation Technique (FOT) can detect impairments of lung function by measuring lung resistance and reactance during normal tidal breathing. A MostGraph is one of the FOT using multi-spectrum oscillation technique, and demonstrates the frequency-dependent and time-dependent respiratory impedance in 3-dimensional graphics.

Methods: We recruited 26 outpatients with stable mild (n=13) and moderate (n=13) COPD at the University of Tokyo Hospital. The impedance of respiratory system was measured by FOT using a MostGraph. Respiratory resistance (Rrs) and respiratory reactance (Xrs) during inspiration and expiration were evaluated at 5 Hz and at 20 Hz of oscillatory frequency.

Results: All indices of respiratory resistance, such as Rrs5 and Rrs20, were slightly higher at 5 Hz and at 20 Hz of oscillatory frequency. The Cv values of regional Rrs, Xrs, and the ratio between the difference of Rrs5max-min and Rrs20max-min were significantly different among the groups (p values: 0.0002 and 0.0047). No differences existed between the young and elderly subjects. The average Rrs, Xrs and the ratio between the difference of Rrs5max-min and Rrs20max-min were significantly different among the groups (p values: <0.0001, <0.001, <0.001 and 0.0054). The highest values were noted in the young subjects, significant differences between the elderly and COPD patients were found for Rrs, Fev1, and Xrs.

Conclusion: EIT is able to detect disease and age related differences in regional lung function. The heterogeneity of lung function is similar in the young and elderly healthy subjects but lower than in COPD patients.

We evaluated the respiratory impedance during inspiratory and expiratory phase of normal breathing in COPD patients.

Methods: We recruited 26 outpatients with stable mild (n=13) and moderate (n=13) COPD at the University of Tokyo Hospital. The impedance of respiratory system was measured by FOT using a MostGraph. Respiratory resistance (Rrs) and respiratory reactance (Xrs) during inspiration and expiration were evaluated at 5 Hz and at 20 Hz of oscillatory frequency.

Results: All indices of respiratory resistance, such as Rrs5 and Rrs20, were slightly higher in moderate COPD than mild, although there were no significant differences. There was a tendency that the ratio between the difference of Rrsmax-min and the difference of Rrs20max-min within tidal breathing was higher in mild COPD than in moderate (p<0.08).

Conclusion: The larger difference in Rrs5-20 during tidal breathing might be useful property to distinguish the severity of COPD.

SUNDAY, SEPTEMBER 25TH 2011
P933
Freeflowmetry – The new method of evaluation of the respiratory function phenotype
Zygmunt Podolec. Physiology and Mechanics of Breathing, Research and Development Centre MEDiNET, Cracow, Poland

Introduction: Freeflowmetry is the new method of air flow and air volume measurement during forced and free breathing through the open or partially closed mouth or through the nose. Application of tight silicone mask connected with dFPP® pneumotachograph allows adaptation of the natural resistance of the oral cavity in order to reduce the airway collapse. The aim of the study was to compare the results of examination performed with dFPP® pneumotachograph with mouthpiece, with the results of examination performed with silicone mask

Method: The examinations were performed using PNEUMO® PC spirometer (absMED, PL) in group of COPD patients: 6 female and 4 male at age of 75±5 years and in control group of healthy: 6 female and 2 male at age 73±6 years.

The results are shown in table 1.

Table 1
<table>
<thead>
<tr>
<th>Method</th>
<th>Spirometric</th>
<th>Freeflowmetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>1.55</td>
<td>0.84</td>
</tr>
<tr>
<td>Control</td>
<td>2.77</td>
<td>2.38</td>
</tr>
<tr>
<td>NS</td>
<td>p=0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

ΔFVC = FVC – FVC; ΔFEV1=FEV1 – FEV1; FVC-CM = measurement of FVC through partially closed mouth; ΔFVC-CM = ΔFVC – FVC.

Conclusion: Freeflowmetric examination can contribute to the optimization and individual adaptation of treatment, the determining of the phenotype of bronchial obstruction and/or airway collapse in common diseases such as COPD and asthma. Further studies are required for the comparison of freeflowmetric test results before and after physical exercise and before and after application of bronchodilator.

P934
Audit of a new mannitol challenge testing service in a UK tertiary centre
Martyn Bucknall. Lung Function Department, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Guy's and St Thomas' NHS Foundation trust (GETT) is a tertiary hospital based in London, UK, offering specialist allergy and asthma clinics. In July 2010, GSTT switched from using histamine to mannitol for performing bronchial challenge testing (BCT). BCT is an essential diagnostic investigation for identifying/excluding asthma and monitoring responses to treatment regimes. We performed an audit of the new service, using mannitol between July 2010 and February 2011. We looked at patient demographics, (age, sex, baseline lung function), test outcomes (i.e. positive, negative, reasons for terminating test, fall in FEV1), sources of referral and clinical reasons for referral to our laboratory.

Table 1 shows patient demographics and baseline lung function. 60 patients were referred to the service (28M, 32F). The mean age was 40.2 yrs.

Table 1: Patient demographics

<table>
<thead>
<tr>
<th>Number (n, %)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs, mean (range)</td>
<td>40.2 (16-70)</td>
<td>40.1 (21-66)</td>
</tr>
<tr>
<td>Baseline FEV1, % pred (range)</td>
<td>95.2 (54-145)</td>
<td>92.0 (55-145)</td>
</tr>
<tr>
<td>SF did not significantly change FEV1% predicted.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD = -0.427, P = 0.016, activity score; r = -0.368, P = 0.042, total score and FVC% predicted (r = -0.534, P = 0.002, activity score; r = -0.504, P = 0.004, total score) in subjects of age less than 70 years. Moreover, SGRQ score was significantly reduced by SF (difference -19.8, 95% CI -28.3 to -11.3; P &lt; 0.001) but not by IS. SF did not significantly change FEV1% predicted.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P935
Tracheal sound level as a potential diagnostic tool for pulmonary obstructive syndromes
Tudor Andrei Cernomaz, Daniela Boisteanu, Raluca Vasiliuta, Traian Mihaiascu. Pneumology, Clinic of Pulmonary Diseases, Iasi, Romania

Aim and objectives: To assess the possibility of developing a tracheal sound analysis tool capable of diagnosing obstructive syndromes.

Material and methods: 34 subjects were stratified to the obstructive or control group. Tracheal sound was recorded during a forced expiratory maneuver; acquired signals were analyzed in terms of sound level vs time and a linear regression model was computed. The obstructive subgroup included 21 vs 13 controls. We found statistically significant between group differences for expiratory duration and for the linear regression and negative significant correlations between slope and expiratory duration, FEV1 and FEV1/VC. Building the ROC curve a threshold value of -19.67 for the slope of the linear regression model will associate a sensitivity of 95% and a specificity of 84.6% for this test.

Conclusion: Available data suggests that tracheal sound level analysis could be developed into a diagnostic and monitoring tool; additional mathematical approaches are probably necessary.

P936
Clinical interpretation of St George's respiratory questionnaire in Chinese COPD patients
Yipeng Du, Rong Liu, Bei He. Respiratory Medicine, Third Hospital of Peking University, Beijing, China Respiratory Medicine, Third Hospital of Peking University, Beijing, China

Background: Although the St George’s Respiratory Questionnaire (SGRQ) was used widely in China as a valid instrument for quality of life evaluation in COPD patients, the relationship between SGRQ, lung function and therapeutic effect is uncertain.

Objectives: To determine whether the SGRQ was related with lung function in Chinese COPD patients and evaluate therapeutic effect on them.

Methods: After a two weeks run-in period, outpatients (63 patients; 10 women; mean age 67.6 years) were assessed at baseline by the SGRQ-MC, clinical data and spirometry. Then patients were treated in a randomised, open-labelled, parallel group trial with either a combination of 50 μg salmeterol and 500 μg fluticasone propionate twice daily (SF, n = 18, mean age 67.4 years) or 2.5 mg ofipratropium bromide and 120 μg salbutamol qartic daily (IS, n = 18, mean age 66.7 years) for 3 months. Results: SGRQ activity score and total score were negatively correlated with FEV1 % predicted (r = -0.427, P = 0.016, activity score; r = -0.368, P = 0.042, total score) and FVC% predicted (r = -0.534, P = 0.002, activity score; r = -0.504, P = 0.004, total score) in subjects of age less than 70 years. Moreover, SGRQ score was significantly reduced by SF (difference -19.8, 95% CI -28.3 to -11.3; P < 0.001) but not by IS. SF did not significantly change FEV1% predicted.

Conclusions: SGRQ was associated with lung function in Chinese COPD patients of age less than 70 years and was valid for evaluating therapeutic effect.

P937
The usefulness of the chronic obstructive pulmonary disease assessment test
Young Hwang, Jong Lee, Ho Kim, Ju Cho, You Kim. Internal Medicine, Gyeongsang University Hospital, Jinju, Kyungnam, Korea

Background: It is important to assess and monitor the patients in management of COPD. Recently the COPD assessment test (CAT) has been developed as a short simple method for assessing and monitoring of the quality of life in COPD patients. The object of this study is to evaluate the usefulness of the Korean version of COPD assessment test (KCAT) for assessing and monitoring COPD patients in Korea.

Methods: The study was included 60 patients with COPD in outpatient clinic. We investigated the frequency of acute exacerbations during a previous year. We also measured the spirometry and distance to walk for 6 minutes and obtained the MMRC dyspnea scale, Korean version of the CAT, and BODE index. To assess the usefulness of KCAT, correlations between KCAT and other methods were evaluated.

Results: The KCAT score was correlated significantly with FEV1% (r=0.323, p=0.012), the frequency of acute exacerbation (r=0.292, p<0.024), MMRC dyspnea scale (r=0.554, p<0.001), BODE index (r=0.380, p=0.003) and 6MWD (r= -0.372, p=0.004). The mean KCAT score was increased according to GOLD stages.

Conclusions: The KCAT were shown to be useful assessment of COPD severity. Therefore the KCAT is easily applicable and simple method for assessment of COPD severity in outpatient clinic in Korea.
P938
Collection of year-round hay fever symptoms using a public website (www.allergieradar.nl)

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Introduction: On average 10-20% of the population in the industrialized world suffers from pollen allergy, also known as hay fever. The geographical distribution and severity of hay fever symptoms in the Netherlands year-round is largely unknown.

Aims and objectives: Our objective was to study whether symptoms collected by an interactive internet platform from participants characterized by an internet questionnaire can provide reliable information on hay fever.

Methods: On May 13 2009 the website www.allergieradar.nl was launched. Participants could register by completing an extensive questionnaire on their hay fever symptoms, doctor diagnosis, etc. Once registered, participants regularly entered their geographical position and their symptoms of nose, eyes and lungs on a scale from 1-10. All data from 2009 (May 13-Dec 31) and 2010 (Jan 1-Dec 31) were stored in a database and analysed.

Results: Approx. 7000 entries with symptoms scores were collected in 2009 and in 2010 by 884 and 491 participants, respectively. More than 80% of the participants reported a doctor diagnosed hay fever. The majority of these participants suffered from nose and eye symptoms (>92%) and approx. 50% (also) from lung symptoms. The daily mean maximum symptom score of these participants correlated with the logarithm of the daily pollen counts (correlation coefficient=0.549; p<0.001)). Analysis of the individual symptoms showed that lung symptoms were more severe during the tree pollen season compared to the grass pollen season. Conclusions: We conclude that these internet symptom scores are a valuable tool in studies on hay fever symptoms in the general population and for the development of hay fever forecasts.

P939
Factors associated with better asthma control in eastern Austria
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Background: Asthma control is an important component of quality of care for asthma patients. The controller-to-total-asthma-medication ratio (CTR) has been evaluated as a reliable asthma control and quality indicator.

Aim: To evaluate the effects of a regional “asthma awareness campaign” during 2008 (patient, pharmacy and physician training) on asthma control.

Methods: We used a database form a central health insurance (BGKK, covering 70% of the population) to select a cohort (n=1158) with an asthma diagnosis according to management guideline. Asthma exacerbations and urgent health care utilization (HCU) at 6 months were recorded.

Results: Results: 379 (120 men) asthmatics completed the study. The ACT cut-off for uncontrolled and partly controlled asthma were ≥19 (sensitivity 0.73, specificity 0.67, correctly classified 69.5) and ≥22 respectively (sensitivity 0.73, specificity 0.71, correctly classified 72.1). Baseline ACT score had an odds ratio of 2.34 (95%CI 1.48-3.69) and 2.66 (1.70-4.18) for urgent HCU and exacerbations respectively at 6 months (p<0.0001). However, baseline FeNO and spirometry values had no association with urgent HCU and exacerbations. For serial changes of ACT scores over 3 months, the cutoff value was best at ≤3 for treatment decisions with low sensitivity (0.23) and ≥3 correctly classified (57.3%) values.

Conclusion: Single measurement of ACT is a useful tool for assessment of asthma control, prediction of exacerbation and changes in treatment decisions.

P940
Asthma control test: Cut off values of control according to GINA guideline and its ability to predict exacerbations and treatment decisions
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1 Department of Internal Medicine, Medical University of Vienna, Vienna, Austria; 2Department of Pulmonology, Leiden University Medical Center, Leiden, Netherlands; 3Department of Internal Medicine, Chinese University of Hong Kong, Hong Kong, Hong Kong

Introduction: This study assessed ACT cut-off values for asthma control according to GINA guideline in adults. ACT score in the prediction of exacerbations and serial changes in ACT score over time in relation to treatment decisions was also assessed.

Methods: Subjects completed ACT together with same-day spirometry and fractional concentration of exhaled nitric oxide (FeNO) measurement at baseline and at 3 months. Physicians, blinded to the ACT scores and FeNO values, assessed the patient’s asthma control in the past month and adjusted the asthma medications according to management guideline. Asthma exacerbations and urgent health care utilization (HCU) at 6 months were recorded.

Results: Results: Among the 14,267 patients with flexible fiberoptic bronchoscopy, 30 patients (0.2%) were diagnosed with TBO. Patients were composed of 17 male and 13 female with a mean age of 60 years. The common symptoms were cough, dyspnea, and hemoptysis. Endotracheal nodules were the most common finding on computed tomography (CT). Osteocartilaginous nodules were mainly present in trachea on bronchoscopy, and the most common type was confluent form. The mean FeNO was 101±50% predicted. Treatment included mostly conservative (n = 29) and then symptoms were considerably relieved in 8 cases but there was no significant improvement noted in 18 patients. 4 patients died on account of associated lung lesion.

Conclusion: In accordance with previous studies, TBO is a rare disease and the diagnosis should be suspected based on CT findings and bronchoscopic examination of the airways. This study demonstrated that conservative treatment according to clinical symptom was effective and showed relatively good clinical outcome.

P941
The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) is a new, simple questionnaire designed to evaluate quality of life in COPD patients. In contrast to more complex assessment tools (such as St. George’s Respiratory Questionnaire), few studies have evaluated its relationship with other disease severity markers in COPD.

In this study we investigated the relationship between CAT score and markers of disease severity in COPD, including forced expiratory volume in 1 second (FEV1), endurance shuttle walk test (ESWT) and incremental shuttle walk test (ISWT).

Results: Fifty patients with a known diagnosis of COPD (male: female ratio 22:28, mean age 68.1±13.3 years, mean FEV1 46.9±20.3% of predicted) were evaluated using spirometry, ESWT and ISWT. Quality of life was assessed using CAT. Mean ISWT was 182.1±124 metres and mean ESWT was 58.0± minutes. CAT score correlated negatively with ESWT (r = -0.401, p = 0.01) and ISWT (r = -0.30, p = 0.05). There was no significant correlation with FEV1 in this study population. However, it is very interesting that CAT score is inversely related to exercise capacity. As the disease gets more severe, quality of life worsens (higher CAT score on CAT exercise capacity) and exercise capacity falls (lower ESWT/ISWT). Although this concept is logical, it was not described prior to this study.

Our study showed that CAT represents a useful instrument to evaluate disease impact in COPD, when interpreted alongside complementary diagnostic information. It would be intriguing to see the relationship between CAT and other parameters of lung function, such as transfer factor and lung volume in future studies.
Epidemiology of bronchiectasis patients had a score of 13, with a FEV of 78.4 ± 18.8% (p < 0.001).

Conclusions: All three groups demonstrated a moderate impairment of the quality of life, showing a significant difference between idiopathic bronchiectasis patients and patients with associated COPD. The association of the two respiratory disease leads to a lower quality of life for these patients. All associated respiratory diseases must be considered when interpreting this questionnaire.

Results: Bronchiectasis and COPD patients with a mean age of 74.4±4.8 years had a 17.7 CAT score, which correlates with a FEV1 mean value of 53.6±10.8% (p < 0.05), posttuberculosis bronchiectasis patients with a mean age of 52.4±16.6 years had a 15.1 CAT score correlated with FEV1 of 66.1±16.9% (p < 0.001), while idiopathic bronchiectasis patients had a score of 13, with a FEV1 of 78.4±18.8% (p < 0.001).

Conclusions: All three groups demonstrated a moderate impairment of the quality of life, showing a significant difference between idiopathic bronchiectasis patients and patients with associated COPD. The association of the two respiratory disease leads to a lower quality of life for these patients. All associated respiratory diseases must be considered when interpreting this questionnaire.

Comparison of health status in stable patients with bronchiectasis due to common variable immune deficiency (CVID), and idiopathic bronchiectasis

Lorraine Ozerovich1, Samantha Pignore2, Winston Bunya3, Robert Wilson1, Noel Snell1, Peter Kelleher1, Jillian Riley4, 5 Host Defence Unit, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; 6 Respiratory Services, St George’s Healthcare NHS Trust, London, United Kingdom; 1 Research Services, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; 2Post-Graduate Education (Nursing), Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom

Background: Patients with CVID develop bronchiectasis (bx) due to damage caused by lung infections. Bx is associated with impaired health status (Wilson C et al Am J Respir Crit Care Med 1997; 156: 536-541). Improved treatment for CVID+bx has led to fewer infections but little is known about impact on health status.

Methods: Patients undertook a Shuttle Walking Test (SWT) and completed the St George’s Respiratory Questionnaire (SGRQ). Scores were compared with data from a previous study of idiopathic bx (Ozerovich L et al Am J Respir Crit Care Med 2004; 169: A330).

Results: 22 patients participated; 9 male (41%); mean age 45 (range 17-67); 20 (91%) on immunoglobulin (lg) therapy. Patients with CVID+bx had better scores for all SGRQ domains, and better SWT, both of which were clinically relevant: SGRQ >4 point difference (Jones P. Eur Respir J 2002; 19: 398-404); SWT 60-115m (Pepin V et al, Thorax 2011;66:115-120), although neither attained statistical significance.

There were no significant correlations between SWT and activity component or SGRQ Total Score (=0.45, p<0.05; = -0.43, p<0.05) in the CVID with bx group.

Conclusion: Patients with bx due to CVID have impaired health status and SWT; scores were generally better than for demographically similar historical controls with idiopathic bx, possibly as a result of specific therapy (lg replacement) in the majority of these patients.

Pan-European data on health status in COPD are scarce. The purpose of the HEED study was to evaluate the health status from a primary care COPD population in seven European Countries (Jones P et al. Health-related quality of life in patients with COPD severity within primary care in Europe. Respiratory Medicine 2010).

We present here the Belgian results of this Pan-European survey.

This cross-sectional epidemiological study in a primary care setting evaluated health status in 394 COPD patients by Belgian primary care physicians using the St George’s Respiratory Questionnaire (SGRQ) and the COPD Assessment test (CAT). The Health-related Quality of Life (HRQoL) scores by GOLD stage, using both the SGRQ and the CAT, are shown in Table 1.

<table>
<thead>
<tr>
<th>CAT Questions</th>
<th>RT + TB</th>
<th>Idiopathic Rx</th>
<th>Rx + COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>3.2</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Pheidem</td>
<td>3.3</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>1.8</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>1.8</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Activities</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Confidence</td>
<td>1.4</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Sleep</td>
<td>1.6</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Eney</td>
<td>2.2</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Total score</td>
<td>16.5</td>
<td>13</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Conclusions: All three groups demonstrated a moderate impairment of the quality of life, showing a significant difference between idiopathic bronchiectasis patients and patients with associated COPD. The association of the two respiratory disease leads to a lower quality of life for these patients. All associated respiratory diseases must be considered when interpreting this questionnaire.
pulmonary disease (COPD). There is no good data to assess the ADL and sleep of COPD subjects in their home environment.

Wrist actigraphy (Actiwatch-Spectrum) was used to evaluate activity in COPD subjects to address the hypothesis that actigraphy is a good method of evaluating ADL and sleep and demonstrate subject compliance. Twelve COPD subjects and twelve age and gender matched controls wore the Actiwatch for fourteen (14) days continuously and the activity data was analyzed for ADL and sleep. Compliance was measured by the built-in “off wrist” detector. Total activity counts/day were significantly lower (p<0.01) in the COPD subjects than Controls: 237,494 ± 22,846 vs. 557,842 ± 36,006, respectively. Activity counts/minute and maximum activity counts were significantly lower (p<0.001) in the COPD subjects; 219 ± 8 vs. 630 ± 58 and 1,560 ± 269 vs. 3,163 ± 862, p<0.01, respectively. Total sleep time in the COPD subjects was significantly reduced (p<0.01); 343 ± 15 minutes vs. 451 ± 19 minutes. Sleep efficiency was decreased in the COPD subjects vs. Controls; 72 ± 3 vs. 88 ± 4 respectively (p<0.05). The minutes of wake after sleep onset was significantly (p<0.01) increased in the COPD subjects from 10 ± 4 minutes to 39 ± 23 minutes. Compliance, % time wearing the Actiwatch, was the same in COPD and Controls; 99 ± 6 ± 0.2%

Activity of daily living and sleep were significantly decreased in the COPD subjects as compared to controls which was extremely high for both groups indicating that wrist actigraphy may be a useful measure in COPD.

P948

Cough ability and oxygen saturation (OS) home monitoring in amyotrophic lateral sclerosis (ALS) patients: Preliminary data

Michele Vitacca. Lumezzane, Brescia, Italy

Background: Cough measure by Peak Cough Expiratory Flow (PCEF) and OS monitoring are crucial in ALS time course.

Purpose: In ALS patients (ALS score < 35, MIP% > 80% and MEP < 100% predicted), cough stratification was done in order to drop out (refuse, death, family problems, care under other health facility) were evaluated: a) feasibility of home daily PCEF and OS measurements b) PCEF and OS changes c) PCEF and OS variation before and during each new respiratory derangement event (RDE).

Methods: The patient/caregiver was requested to measure every day PCEF and OS and to annotate RDE.

Result: 10 patients were enrolled. Two patients refused to start the project when at home. Eight patients measured PCEF and OS for 185 ± 173 consecutive days (range 13 – 431 days) making a 1,246 measurements. Six out 8 patients dropped-out; daily feasibility worsened from 80% in the first week to 25% at the end of the study; completion rates was 86.3% (range 38 -100%). Out of 8 patients showed 6 strong RDE. PCEF daily decay (PDD) was 1.29 ± 0.2% per day. No statistically significant changes in OS were found (from 95.25 ± 1.3 to 95.13 ± 1.71).

Conclusions: On this preliminary data, we can say that cough measurement is feasible, safe and reliable in ALS home environment.

P949

Who win? Spirometry versus symptoms for predicting the longitudinal outcomes in COPD patients – 10 years observation

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The spirometric criteria for COPD diagnosis is the king of the gold standard and GOLD-guide accepted in diagnosis, treatment, follow, and disease prediction. Unfortunately, little attention has been paid on the importance of respiratory symptoms in the prognosis of the disease.

Aim: To evaluate whether spirometric criteria are associated with long term clinical outcomes in COPD patients with or without chronic symptoms. In 2000-2001, 2756 non asthmatic participants in the ECRHS (20-44 years) were classified according to smoking history, GOLD criteria and presence or absence of chronic symptoms. In 2000-2001, 2756 subjects were studied. Asthma clinical severity was measured in using asthma control test (ACT) and evidence for GERD was verified using standard questionnaire. Spirometry, impulse oscillometry, and lung volume studies (using body plethysmograph and IOS both provide by Jaeger, Germany) were performed. The difference between total airway resistance (TAWR) indicated by resistance at 5Hz and central airway resistance (CAWR) as indicated by resistance at 20 Hz in oscillometry was calculated as representative of resistance of peripheral airways (PAWR). The relationship between the symptoms of GERD, ACT score and parameters of lung function were analyzed.

Results: PAWR and TAWR were both significantly higher in asthma patients with GERD symptoms than patients without GERD symptoms (mean ranks of 55.8 versus 43.0 kpL/s; p=0.04, respectively). However, the best fit for the analysis of joint data was the logistic regression revealed that the odds ratio (OR) of chronic daily headache for subjects with GERD was 2.0 (95% CI 1.1-3.71). In the subgroup of non-smokers, the OR was 2.7 (95% CI 1.34-5.42).

Conclusion: Subjects with asthma had a higher risk of chronic daily headache than subjects without asthma in this population-based study. Asthma may be related to chronic daily headache.

P951

Effect of GERD on clinical severity and functional characteristics of lung function in asthma

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Background: It is known that almost one third of patients with asthma have symptomatic evidence for coexisting gastroesophageal reflux disorder (GERD) which is thought to be aggravating factor in asthma.

Aims and objectives: We investigated the impact of coexisting GERD on the severity and functional characteristics of asthma.

Method: Ninety-two patients with asthma diagnosed on the basis of ATS criteria were studied. Asthma clinical severity was measured in using asthma control test (ACT) and evidence for GERD was verified using standard questionnaire. Spirometry, impulse oscillometry, and lung volume studies (using body plethysmograph and IOS both provide by Jaeger, Germany) were performed. The difference between total airway resistance (TAWR) indicated by resistance at 5Hz and central airway resistance (CAWR) as indicated by resistance at 20 Hz in oscillometry was calculated as representative of resistance of peripheral airways (PAWR). The relationship between the symptoms of GERD, ACT score and parameters of lung function were analyzed.

Results: PAWR and TAWR were both significantly higher in asthma patients with GERD symptoms than patients without GERD symptoms (mean ranks of 56.6 versus 41.9; p=0.01 and 55.8 versus 43.0 kpL/s; p=0.04, respectively). However, the values for ACT score, FEV1, FVC, PEF, RV, TLC, FRC/TLc were not significantly different in these two groups.

Conclusion: Clinical severity of asthma measured by ACT score is not different in asthma patients with and without GERD symptoms and central and peripheral airway resistance is equally influenced by symptomatic GERD.

P952

Six-minute walk test: Comparison with cardiopulmonary exercise test performance, lung function and arterial blood gases in patients with bronchiectasis

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Background: Relationships between the 6-minute walk test (6MWT) and car-
diopulmonary exercise test (CPET) performance have been established in some respiratory diseases. However, in patients with bronchiectasis (BECTs) data are scarce in the literature.

**Aims:** To evaluate relationships between 6MWT distance and CPET performance, lung function (LF) and arterial blood gases (ABG) in patients with stable bronchiectasis.

**Methods:** A retrospective evaluation of 27 patients with BECTs who attended a rehabilitation program and who had 6MWT, CPET in cycle ergometer, LF and ABG (at rest) evaluation at the start of the program. Spearman’s correlation coefficient was used for statistical analysis.

**Results:** Thirteen male and 14 female with ages ranging from 19 to 75 (median 51 yrs). Sixteen patients were severely obstructed and 11 had airway colonisation. Mean 6MWT distance was 440.4 meters and mean end test saturation was 89.30%. Mean maximal work (MW) was 68.1 Watts and mean end-CPET saturation was 89.37%. Positive correlations were found between 6MWT distance and MW (r=0.721**, p<0.000), VO2max (r=0.551**, p<0.003), VO2max/kg (r=0.497**, p<0.008), PaO2 (r=0.485*, p<0.010) and HgbSat (r=0.481*, p<0.013). No correlations were found between 6MWT distance and FVC, FEV1, FEV1/FVC, residual volume or PaCO2. Considering colonised patients, positive correlations were found between 6MWT distance and VO2max, VO2max/kg, PaO2 and HgbSat at the 0.05 level.

**Conclusions:** 6MWT is a simple test that seems to mirror exercise capacity evaluated by CPET in patients with bronchiectasis. None of the LF parameters evaluated reflected 6MWT distance in these patients.

**P953**

Leicester cough questionnaire and sputum colour chart assessment in non-cystic fibrosis bronchiectasis: A cohort analysis


**Introduction:** Murray et al. showed that Leicester Cough Questionnaire (LCQ) correlates with disease severity. Sputum colour chart (SCC) assessment was associated with bacterial colonization, bronchiectasis severity and FEV1. We investigated these clinical tools in a cohort of non-cystic fibrosis bronchiectasis (NCFB).

**Methods:** 63 patients (27male, 59±18 y) with NCFB were recruited. Underlying etiologies of NCFB were analyzed and each patient was evaluated by means of spirometry and LCQ. Exacerbation rate and retrospect sputum culture results were analysed. Sputum was induced with hypertonic saline inhalation, total/differential cell count and SCC of sputum were assessed and IL-8, MCP1, b-2 microglobuline, NSE and TNF-a were measured.

**Results:** Patient sputum purulence prediction correlated significantly with SCC evaluated by the doctor (p<0.0001, r=0.72). LCQ and subcores correlated significantly with SCC (p=0.0004, r=-0.37) with more cough impact in more purulent spuata. LCQ total and subcores all correlated significantly with total number of bacteria found in retrospective sputa with worse symptoms in patients with more bacteria found (p<0.01, r=0.32). The SCC also correlated with number of cells in sputum cell count (p<0.0001, r=0.66). IL-8 (p<0.0001, r=0.61) and TNF-a (p=0.0002, r=0.43). Finally, we saw worse FEVI in patients with more purulent sputa (9%; p=0.30, r=-0.37).

**Conclusion:** Patient SCC prediction correlated with doctor SCC evaluation. LCQ, subcores and SCC correlate with lung function, presence of bacteria in all sputa and severity of airway inflammation. We conclude that LCQ and SCC are concise tools and should be used in follow-up of NCFB.

**101. Animal models of airway inflammation**

**P954**

T cell clone transfer model for steroid resistant asthma

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**Background:** Glucocorticoid (GC) action on asthma has been partly explained by the inhibition of T cell activation. We analyzed the steroid sensitivity of ovalbumin (OVA) reactive helper T (Th) cell clones both in vitro and in vivo.

**Methods:** Th clones were cultured with antigen presenting cells, OVA, and various concentrations of dexamethasone (DEX). The proliferative response of each Th clone was measured by 3H-thymidine uptake. For in vivo experiments, unprimed BALB/c mice were transferred with Th clones, challenged with OVA, and administered with DEX subcutaneously. The number of infiltrating cells in bronchoalveolar lavage fluid (BALF) was measured.

**Results:** Six Th clones were classified into steroid sensitive and steroid resistant clones in terms of the effects of GC on the proliferative responses analyzed in vitro. Airway infiltration of eosinophils and lymphocytes of mice transferred with steroid sensitive clones were effectively inhibited by the administration of DEX. In contrast, those of mice transferred with steroid resistant clones were not significantly inhibited by DEX, except that the number of eosinophils in the BALF of mice transferred with one steroid resistant clone, Ts-1, was only partially reduced.

**Conclusion:** Steroid sensitivity of Th clones measured in vitro were consistent with that of adoptively transferred asthma model measured in vivo. Steroid sensitive and resistant asthma models seem valuable for understanding the mechanisms of steroid resistance in severe asthma.

**P955**

PARP-1 deficiency blocks IL-5 expression through calpain-independent degradation of STAT-6 in a murine asthma model

Amarjit Naura1, Rahul Dutta1, Mourad Zerfai2, Yousser Errami2, Mustapha Oumounna1, Hogyoun Kim1, Jiang Ju1, Virginia Ronchi1, Arthur Hass2, Hamid Boulares1.

**Introduction:** We recently showed that poly(ADP-ribose)(polymerase-1 (PARP-1) may play a role in allergic (ovalbumin)-induced airway eosinophilia, possibly through a specific effect on IL-5 production.

**Objective:** To explore the mechanism by which PARP-1 regulates IL-5 production in asthma.

**Methods:** This study was conducted using a murine model of allergic airway inflammation and primary splenocytes.

**Results:** PARP-1 knockout-associated reduction in IL-5 upon allergen exposure occurs at the mRNA level. Such an effect appears to take place after IL-4 receptor activation as PARP-1 inhibition exerted no effect on JAK1/JAK3 activation.

**Conclusion:** These results demonstrate a novel function of PARP-1 in regulating IL-5 expression during allergic-induced inflammation and explain the underlying mechanism by which PARP-1 inhibition results in IL-5 reduction.

**P956**

Function of cAMP response element modulator in a murine asthma model

Eva Verjans1, Kathleen Resse2, Norbert Wagner1, Stefan Uhlig2, Lisa Tennbeck2, Christian Martini2.

**Introduction:** Several isoforms of the cAMP response element modulator (CREM) act as transcriptional repressors or activators binding to the cAMP response element of different promoters. In contact dermatitis we previously demonstrated the importance of CREM for antigen presenting cell-dependent and independent T cell function and termination of T cellular immune response. In this study we investigated the role of CREM in murine ovalbumin (OVA)-induced airway inflammation.

**Method:** Male wild type (WT) and CREM knockout animals (CREM-KO) were sensitized i.p. with 10^5 OVA, and administered with DEX subcutaneously. The number of infiltrating Th2 cells was measured.

**Results:** Th clones were cultured with antigen presenting cells, OVA, and various concentrations of dexamethasone (DEX). The proliferative response of each Th clone was measured by 3H-thymidine uptake. For in vivo experiments, unprimed BALB/c mice were transferred with Th clones, challenged with OVA, and administered with DEX subcutaneously. The number of infiltrating cells in bronchoalveolar lavage fluid (BALF) was measured.

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**Method:** Male wild type (WT) and CREM knockout animals (CREM-KO) were sensitized i.p. with 10^5 OVA in aluminum hydroxide solution (day 0, 14 and 21) and with aerosol (1% OVA on day 28 and 29). On day 35 bronchial responses to nebulized acetylcholine (0.001-1mg) were examined using the flexVent system (SCIREQ, Montreal, Canada). Inflammatory responses were evaluated by cell counts, cytokine- and IgE measurements in bronchoalveolar lavage (BAL) and serum. Changes in lung tissue were investigated by histology and calculation of the wet/dry ratio.

**Results:** CREM-KO mice showed an increase in airway responsiveness by elevation in central airway (177%) and tissue resistance (214%) compared to WT (100%). In addition, higher numbers of eosinophils and lymphocytes as well as upregulated Th2 cytokines were found in the BAL of CREM-KO mice. Lung histology indicated increased pulmonary cell infiltration, stronger mucus production and goblet cell hyperplasia.

**Conclusion:** CREM deficiency drives Th2 immune response and influences airway tone as well as mucus production. Our findings suggest that the presence of CREM at least partially protects from the development of asthmatic disease by immunological and non-immunological mechanisms.
P957

Control of allergen-induced inflammation and hyperresponsiveness by the metalloproteinase ADAMTS-12

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Background: ADAMTS (A Disintegrin And Metalloproteinase with Thrombospondin motifs) constitute a family of endopeptidases related to gaffins metalloproteinases (MMPs). These proteases have been largely implicated in tissue remodeling associated to pathological processes. ADAMTS-12 has been identified as an asthma-associated gene in a human genome screening program.

Objective: To investigate potential roles of ADAMTS-12 in experimental models of asthma.

Methods: In our study, two different in vivo protocols of allergen-induced asthma were applied to the recently generated ADAMS-12-deficient mice, and corresponding wild-type mice.

Results: The results obtained provided evidence for a protective effect of this enzyme against bronchial inflammation and hyperresponsiveness. In the absence of ADAMS-12, challenge with allergen (ovalbumin and house dust mite) led to exacerbated eosinophilic inflammation in the bronchovascular lumen ( BALF) and in lung tissue, along with airway dysfunction assessed by increased airway responsiveness following methacholine exposure. Furthermore, mast cells counts, ST2 receptor, and IL-33 levels were higher in the lungs of allergen-challenged ADAMS-12-deficient mice.

Conclusion: The present study provides the first experimental evidence for a contribution of ADAMTS-12 as a key mediator in asthma, interfering with immunological processes leading to inflammation and airway hyperresponsiveness.

P958

Local inhibition of IL-4 and IL-13 protects lung function in OVA mouse model

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DARPinSTM (Design Ankyrin Repeat Proteins) are a novel class of proteins that combine the affinity and specificity properties of antibodies with the solubility and tissue penetration properties of small molecules. The excellent biophysical properties of DARPin domains allows for simple engineering of multispecificity by linking domains that target different ligands. DARPin134 is a bispecific DARPin that inhibits binding of murine IL-13 and IL-4 to their receptors.

The bispecific molecule (DARPin134) or either of the mono-specific molecules was delivered to the lungs of mice via intra-tracheal instillation during an acute ovalbumin sensitization and challenge model. Free IL-4 and IL-13 levels were reduced in the BAL following treatment with DARPin134. While the anti-IL-4 and anti-IL-13 DARPin each showed a trend towards reducing eosinophils in the lungs of mice, the bispecific DARPin significantly reduced eosinophil infiltration.

In addition, an improvement airway hyper-responsiveness in mice treated with DARPin134 was observed.

A variety of studies have confirmed the unique and overlapping roles for IL-13 and IL-4 in the development of allergic asthma.

P959

Effect of dietary nitrite and nitrated fatty acids on airway hyperresponsiveness and inflammation in a mouse model of asthma

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Dietary nitrite (DN) generates NO that lowers blood pressure in vivo. Nitrated fatty acids (FAs) are produced endogenously from nitrated dietary polyunsaturated fatty acids and display broad anti-inflammatory effects including protection in an in vivo model of inflammatory bowel disease.

Our aim was to investigate if DN or NO2-FAs affect airway hyperresponsiveness and inflammation in a mouse model of asthma.

Female BALB/c mice were sensitized with OVA/Al(OH)3 on day 0 and 7 and challenged with OVA or PBS i.n. on day 14-16. DN was administered day 10-17 by a s.c. placed osmotic pump. Airway resistance (Rs) to metacholine and inflammatory cells in bronchoalveolar lavage (BAL) were determined on day 17.

DNA induced an increase in Rs compared to control in all groups (OVA vs. PBS: 3.3±0.2 vs. 2.3±0.1 μL, OVA-DN vs. PBS: 5.6±0.2 vs. 2.5±0.1, OVA-NO2-FAs vs. PBS: 5.4±0.2 vs. 2.2±0.1 (cmH2O/mL), all p<0.01). No differences in Rs were observed between the OVA groups with or without administration of DN or NO2-FAs (p>0.05). OVA induced an increase in BAL eosinophils (EOS) compared to control in all groups (OVA vs. PBS: 25.5±5.5 vs. 0±0, OVA-DN vs. PBS: 21±4 vs. 0±0, OVA-NO2-FAs vs. PBS: 45±7 vs. 0±1 (10,000 cells/mL), all p<0.001). No differences in EOS were observed between OVA with or without administration of DN or NO2-FAs (p>0.05). The number of EOS was higher in OVA-NO2-FAs treated animals versus OVA alone (p<0.001).

To conclude, neither DN nor NO2-FAs displayed anti-inflammatory effects in this asthma model, indicating that there is tissue specificity in the actions of these reactive nitrogen oxide species.

P960

Influence of acid sphingomyelinase deficiency in a murine model of allergen-induced asthma

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Introduction: Acid sphingomyelinase (ASM) deficiency causes lipid storage diseases, called Niemann-Pick disease (NPD) type A (neuronopathic) and B (non-neuronopathic). Previous studies demonstrated an association of NPD type B with respiratory failure and lung infections. We investigated the role of ASM deficiency in a murine model of allergic asthma.

Method: Male C57BL/6 (WT) and ASM knockout mice (ASMO) were intraperitoneally sensitized with ovalbumin (OVA)/Alum (1μg/1.5mg) on days 0, 1, 2, and 3. Repeated aerosol challenges (1% OVA) followed for five weeks on two consecutive days every week. Bronchoalveolar lavage (BAL) serum and lung tissue were taken for cell counts, cytokine measurements, histology slides and collagen depositions. Precision-cut lung slices (PCLS) were prepared to investigate early asthmatic response (EAR).

Results: Edema formation was less in ASMO-KO (73.6±7.6%) compared to WT. In addition, sensitized ASMO-KO showed significantly higher cell numbers in BAL and lung tissue primarily consisting of neutrophils and enlarged macrophages, whereas numbers of eosinophils were similar. The ratio of eosinophils and neutrophils was characteristic of a typical Th2-pattern. Differences in cytokine and chemokine levels in BAL and serum were not found. OVA stimulation of PCLS from both mouse strains resulted in a weak bronchoconstriction.

Conclusion: ASM-KO showed the typical characteristics of NPD, but their allergic inflammation was similar to that of WT mice, except for an increased neutrophil/eosinophil ratio. The major observation was reduced edema formation in ASMO-KO mice. We conclude that ASM contributes to allergic edema formation, a key feature of asthma.

P961

Modulation of oral tolerance on the oxidative stress responses in distal lung parenchyma of guinea pigs with chronic allergic inflammation

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Rationale: We previously had shown that oral induced tolerance contributes to reduce distal lung responsiveness, inflammation and remodelling (Nakashima et al.,2008) in a model of chronic inflammation in guinea pigs (GP). In the present study, we evaluated if these responses were associated to alterations on the oxidative stress responses in distal lung.

Methods: GP were submitted to multiple inhalations of ovaalbmin (OVA) or normal saline (NS) (25µl/wk/4wks). At the same oral period tolerance was induced by offering GP ad libitum 2% ovalbumin in sterile drinking water during 4 weeks (OVA-T1) or starting oral ovalbumin after the 4th inhalation of ovalbumin (OVA-T2). Afterwards, lungs were removed, strips of distal lung were stained for iNOS and PGF2ααla (isoprostane) and analysed by morphometry.

Results: In OVA group there was an increase in the iNOS positive cells (20.7±1.9/106·μm²) and PGF2ααla content (17.5±1.2%) compared to NS group (p<0.05). There was a decrease in iNOS positive cells in T1 (12.8±1.9/106·μm²) and T2 (14.3±2.1/106·μm²) compared to OVA (p>0.05). Considering PGF2ααla content, there was a decrease in T1 (6.17±0.4%) and T2 (5.81±0.7%) compared to OVA (p<0.05).

Conclusion: Oral tolerance attenuates the oxidative stress responses in distal lung in this animal model of chronic pulmonary inflammation. These results may clarify the mechanisms involved in the attenuation of mechanical responsiveness, inflammation and remodeling of distal lung by oral tolerance, as previously shown in this animal model. Supported by: FAPESP, CNPq, LIM-20-HC-FMUSP.
**P962**

**AQP5 role in ovalbumin-induced airway inflammation and secretion of MUC5AC in mice**

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**Background:** Airway inflammation and mucus hypersecretion are two important characteristic features of the pathogenesis of asthma. Aquaporin5 (AQP5) is known to be a water channel protein expressed widely in lung epithelium and submucosal glands.

**Objective:** The present study aimed at investigating the involvement of AQP5 in asthma.

**Methods:** The ovalbumin (OVA)-induced allergic pulmonary inflammation and MUC5AC production were examined in AQP5+/+ or AQP5−/− mice. The expression of AQP5s in lung tissue and their regulation were detected. In addition, epidermal growth factor receptor (EGFR) expression and osmotic water permeability in lung were evaluated.

**Results:** Lower expression of AQP1, 4, 5 while higher AQP3 was significant in lung tissue from AQP5−/− model mice. Only AQP1 and AQP5 were up-regulated by anti-asthmatic agents (dexamethasone, ambroxol and terbutaline) significantly. However, AQP5 knockout had significantly low airway inflammation and less lung edema induced by OVA, as compared with those in AQP5+/+ mice. In addition, lower expression of MUC5AC in airway epithelium, less secretion of MUC5AC were found in AQP5−/− model mice. Moreover, the expression of EGFR on airway epithelium was prevented by AQP5 knockout in asthmatic model.

**Figure legend:**
- (A) Lung histology pictures. Body weight was measured by immunochemical staining and quantification.
- (B) Score of staining for MUC5AC expression.
- (C) MUC5AC mRNA expression.
- (D) Osmotic water permeability.

**Conclusion:** Our data indicate that AQP5 is involved in the development of allergic airway inflammation and mucus hypersecretion by regulating osmotic water permeability and expression of EGFR.

**P963**

**Effects of increase gradual OVA doses in the inhalations in a model of asthma to long term**

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Mice are used to develop models of pulmonary allergic disease.

**Objective:** To evaluate the increase gradual OVA doses in a protocol of experimental asthma.

**Methods:** Balb/c mice male were divided in Groups: Control, OVA1%, OVA3%, OVA5%. Sensitized animals received i.p.(OVA+Saline:3x wk/30min). Days: 0,14,28,42. Inhalations sessions (OVA+Saline:3x wk/30min) were performed between 21st and 54th day. The OVA1% group received inhalation with concentration of OVA1%. The OVA3% began with 1% for 3 weeks (wk), in the 4th wk was increased for 3%. The OVA5% began with 1% in the 1st wk, 2nd wk was increased for 2%, 3rd wk with 3%, 4th wk for 4%, 5th wk for 5% of OVA. The Control group received i.p. and Saline inhalations.

**Results:** IgE and IgG1 were increased in sensitized groups, but in the groups 3% and 5% the levels were highest and shown increased of cell migrations presented increase of eosinophils, neutrophils and trickiness of the smooth muscle when compared with others two groups (p<0.01), just Group 3% shown high index of peribronchial eosinophils (p<0.01).

**Conclusions:** Groups OVA3% and OVA5% are more efficient for develop features of experimental asthma, and seems that Group OVA3% develop important increase of eosinophil migration in the airways.

**P964**

**Chronic airway inflammation alters the peripheral distribution of transferred mast cells in deficient C57BL/6-Ki/t-W/-/mice**

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**Objective:** Mice are used to develop models of pulmonary allergic disease. Chronic airway inflammation (CAI) can be induced by ovalbumin (OVA). We addressed this issue by comparing MC-distribution in wild-type C57BL/6 (WT), Wsh (MC-deficient) and intravenously BMMC-transferred Wsh (Wsh+MC) mice.”

**Methods:** In control mice, number of MC in the lungs was significantly higher in Wsh+MC mice. MC in WT mice were located around the central airway (CA) and perivascular space (PVS) whereas they were negligible in parenthesis (PA) and smaller airways (SA). In contrast, MCs in Wsh+MC mice were predominantly found in PA (16±1±2) and PVS (15±2±2) but also around CA (3±1±1) and SA (3±1±1). Induction of CAI in Wsh+MC mice caused increased MC number in the PA (28±6 vs. 16±2) and decreased MC number in the CA (0±1 vs. 3±1) and PVS (5±1 vs. 15±2) compared to controls. Important, these findings suggest that MC transfer causes a completely different condition, which might not be comparable to the WT and thus not serve as an adequate control. Instead,
WshrMC mice may be more suitable in experiments for studying CAAl, since mast cell number, distribution and relocation in response to inflammation more closely resemble findings in the human lung.

**P965**

Effects of chronic allergen exposure on the airway hyperreactivity in sensitized rats

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We aimed at investigating whether chronic allergen exposure (CAE) leads to the development of tolerance or enhances the airway hyperreactivity (AH) in sensitized rats. The airway resistance (Raw) was determined from the total respiratory system impedance under the control condition and following iv methacholine provocations (MCh 2-16 μg/kg) to establish the basal lung responsiveness. The rats were then sensitized to ovalbumin (OVA) and were assigned into two groups: the rats in Group CAE (n=6) were exposed to aerosolized OVA three times a week throughout the study period, while the OVA was withdrawn during the entire protocol in the rats enrolled in Group A (n=8). Assessment of lung responsiveness was repeated in both groups in an identical manner on weeks 3, 6 and 9. The equivalent dose of MCh causing a 20% increase in Raw (ED20) was calculated from each challenge. OVA sensitization was proved to induce AH on week 3 in Groups CAE and A (decrease in Raw of 33±14% and 40±7%, respectively). The subsequent OVA exposure affected significantly the MCh responsiveness with sustained decreases in ED20 on week 6 in Group A and gradual return to normal on week 9, whereas the ED20 in Group CAE was similar to the initial on weeks 6 and 9.

Our findings demonstrate a diminishment of AH following CAE suggesting its favourable influence on the reduction of an existing AH after allergic sensitization. Supported by grant OTKA K81179.

**P966**

Poly IC treatment causes fatal AHR in sensitized mice

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Respiratory infections are known to promote airway hyperresponsiveness (AHR) in asthmatic patients. Toll-receptors (TLRs) are parts of the innate immune system that recognize viral and bacterial components. This in vivo study explores the relation between TLR activation and AHR in a model of allergic airway inflammation.

Female BALB/c mice where sensitized on day 1 and 8, then challenged with either ovalbumin (OVA) or PBS on day 15-17. PolyIC activating TLR3, LPS triggering TLR4 or PBS were then given i.n. during 4 consecutive days. On day 22 the outcome of metacholine (Mch) induced airway resistance was investigated with flexiVent® technique. Cells and inflammatory mediators were analysed in bronchoalveolar fluid (BALF).

PolyIC and LPS treated mice developed a marked AHR not seen among control mice. The airway resistance reached critically high levels in mice concomitantly challenged with OVA (Raw at 1mgMch/kg: PBS: 2.1±0.1, PBS-LPS: 2.9±0.3, PBS-polyIC: 3.6±0.2, OVA: 5.6±0.2, OVA-LPS: 9.3±0.6 and OVA-polyIC: 7.3±0.5 cmH2O·l−1·s−1). The OVA-polyIC mice also displayed circulatory collapse (p<0.05). PolyIC increased the amount of lymphocytes and LPS neutrophils in BALF. Multivariate analysis of a panel of inflammatory mediators could not reveal a clear separation between PBS and OVA groups. However, polyIC treatment induced a specific increase of IL-12 and KC in both treatment groups. Costimulation with PolyIC and LPS, representing viral and bacterial activation, respectively, caused AHR above the effect of OVA which in by polyIC caused fatal circulatory response. It is therefore tempting to suggest that TLRs might play a vital role in virus-induced exacerbations of allergic asthma.

**P967**

The influence of female sex hormones on the number of alternatively activated lung macrophages and airway inflammation in a mouse model of asthma

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The chance of developing asthma increases in girls during puberty. A role for sex hormones has been suggested. Recently we have shown that alternatively activated macrophages (aAM) contribute to the development of asthma in female mice. Here we have investigated how sex hormone depletion before puberty affects asthma in mice and whether this correlates with aAM numbers in lung.

Female Balb/c mice were ovariectomized (OVX) or sham treated before puberty. OVX animals were left untreated, received a 0.1 mg estrogen (E2) pellet, or a 15 mg progesterone (PG) pellet at the day of OVX (all groups n=8). Four weeks later, mice were sensitized i.p with ovalbumin (OVA) and challenged with 1% OVA on days 1 and 14-20. On day 21, allergic inflammation (OVA-specific IgE, eosinophils) and aAM numbers were assessed.

Ablating sex hormones before puberty significantly increased airway inflammation as judged from higher eosinophil numbers in bronchoalveolar lavage fluid and higher OVA-specific IgE levels in serum. aAM numbers were unaffected by OVX. Treating OVX mice with E2 significantly reduced eosinophilic airway inflammation with a concomitant reduction in aAM numbers, whereas PG did not change airway inflammation or aAM numbers.

This study surprisingly shows that OVX in mice before puberty amplifies OVA-induced airway inflammation. This is a consequence of E2 depletion since PG substitution does not reduce the increased allergic inflammation while E2 substitution does. Our data also shows that the effect of OVX does not involve aAM, whereas reduction of eosinophilic airway inflammation after E2 substitution appears to involve aAM.

**P968**

Transcription factor FOXP3 is over expressed in BALT of systemic sclerosis model induced by collagen V nasal tolerance

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**Background:** To evaluate the transcription factor FOXP3 expression in lymphocytes of bronchoconstricted-allergic asthma tissue (IR) and skin when compared with 33,3% of CT (p=0,03) group. In the pulmonary inflammation and the amounts of collagen in pulmonary interstitium of systemic sclerosis (SSc) model after type V collagen (COL V)-induced nasal tolerance.

Methods:** Female New Zealand rabbits (N=12) were immunized with 1mg/ml of COL V in Freund’s adjuvant (IM). After 150 days, six animals were tolerated nasally with COL V (25 μg/day) (IM-TOL), daily during 60 days. Animals (N=6) not immunized and COL V tolerated served as control (CT). Immunohistochemistry and morphometric analysis was used to evaluate the T lymphocytes FOXP3 expression in BALT structures and inflammatory cells in pulmonary interstitium. Types I, III and V collagen expression were evaluated by Real-time PCR.

**Results:** We observed the BALT lymphocytes FOXP3 expressed in all of IM-TOL animals when compared with 33,3% of CT (p=0,03). In the pulmonary interstitium, IM-TOL presented a significant decreased of lymphocytes (4.3±1.1 to 1.7 ± 1.15±1.5±2.53), macrophages (5.73±3.2×7.7 vs. 7.66±1.5) and monocytes (1.91±5.7±3.2 vs. 2.73±7.32) when compared with IM. COL (0.1±0.07 vs. 1.00±0.25, p=0.002) and COLV (1.12±0.42 vs. 4.74±2.25, p=0.009) mRNA expression were reduced in IM-TOL when compared with IM.

**Conclusions:** COL V induced nasal tolerance in the experimental SSc induced FOXP3 regulatory T cells in BALT which can trigger an immune regulatory mechanism resulting in decreased inflammation and collagen expression. It suggests that tolerance with COL V could be a promising therapeutic option for human scleroderma treatment.

**P969**

The respiratory allergen glutaraldehyde in the local lymph node assay: Sensitization by skin exposure, but not by inhalation

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Previously, a selection of low molecular weight contact and respiratory allergens had tested positive in both a skin and a respiratory local lymph node assay (LLNA), but formaldehyde was negative for sensitization by inhalation. To investigate whether this was due to intrinsic properties of aldehyde sensitizers, the structurally-related allergen glutaraldehyde (GA) was tested. BALB/c mice were

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Exposed by inhalation to 6 or 18 ppm GA (respiratory LLNA), both generated as a vapor and as an aerosol. Other groups received 0.25% or 2.5% GA on the skin of the ears (skin LLNA). Lymphocyte proliferation and cytokine production were measured in the draining lymph nodes. GA was positive in the skin LLNA and its cytokine profile (IL-4: IFN-γ) skewed towards a Th2-type immune response with increasing dose. Inhalation exposure did not result in increased lymphocyte proliferation or increased cytokine levels, despite comparable tissue damage (irritation) in the skin and respiratory tract. We hypothesize that the highly reactive and hydrophilic GA oligomersizes in the protein-rich mucus layer of the respiratory tract, which impedes sensitization but still facilitates local irritation. Within the context of risk assessment in respiratory allergy, our results stress the importance of prevention of skin – besides inhalation – exposure to aldehydes like GA.

Conclusions: Our data indicate that overexpression of Prdx6 prevent allergic airway inflammation and hypersecretion by reducing ROS levels. While due to several compensatory mechanisms, targeted disruption of Prdx6 fails to increase OVA-induced asthma.

P970

Overexpression of peroxiredoxin 6 protect mice from ovalbumin-induced airway inflammation and hypersecretion of MUC5AC by reducing ROS levels

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Background: Oxidative stress plays an important role in the pathogenesis of asthma. Peroxiredoxin 6 (Prdx 6), as a newly identified peroxidase, protect cell or organ from reactive oxygen species (ROS)-induced oxidative stress.

Objective: The present study aimed at investigating the involvement of prdx 6 in asthma.

Methods: The ovalbumin (OVA) - induced allergic airway inflammation and MUC5AC production were examined in wild-type (WT), overexpressing (Prdx 6) and control (Prdx 6 null) (Prdx 6-/-) mice. The level of inflammatory cells in bronchoalveolar lavage fluid (BALF) were evaluated.

Results: The expression of Prdx 6 was reduced significantly and up-regulated by dexamethasone and bronchoalveolar lavage from WT mice. Prdx 6+/+ mice had significantly low airway inflammation, low levels of IL-13 in BALF as compared with those in WT mice. In addition, lower expression of MUC5AC in airway inflammation and hypersecretion by reducing ROS levels in bronchoalveolar lavage fluid (BALF) were evaluated.

Conclusions: Our data indicate that overexpression of Prdx 6 protect allergic airway inflammation and hypersecretion by reducing ROS levels. While due to several compensatory mechanisms, targeted disruption of Prdx 6 fails to increase OVA-induced asthma.

P971

Crucial role of phospholipase Cε in the development of asthma in mice

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Phospholipase Cε (PLCε) is an effector of Ras and Rap small GTPases. Studies using genetically-modified mice of PLCε have shown its crucial role in skin inflammation. The purpose of this study is to examine whether PLCε is involved in the pathogenesis of inflammation in the respiratory system. First, we analyzed the location of PLCε in the respiratory system. By immunohistochemical analyses, we found that PLCε is expressed highly by alveolar epithelial cells and moderately by bronchial epithelial cells and smooth muscle cells in the bronchioles and the pulmonary arteries. Next, we experimentally induced asthma in PLCε-/- and PLCε+ + mice in the C57BL/6 background by sensitization with ovalbumin (OVA) followed by boost with OVA by inhalation, and performed pathological analyses at 24 h after the last inhalation. Pathohistological studies of the sections of the lung and bronchi showed that infiltration of leukocytes and mucus production by the goblet cells were greatly suppressed in PLCε-/- mice. Also, characterization of inflammatory cells in bronchoalveolar lavage fluid demonstrated that the infiltration of leukocytes, particularly that of eosinophils, was suppressed in PLCε-/- mice. On the other hand, the serum levels of IgG and IgE specific for OVA were not affected by PLCε-deficiency. These results suggest that PLCε has a crucial role in the pathogenesis of asthma and that PLCε would become a molecular target for the treatment of patients with allergic asthma.

P972

Grape seed proanthocyanidin extract attenuates airway inflammation and hyperresponsiveness in a murine model of asthma: Downregulating inducible nitric oxide synthase

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Background: Allergic asthma is characterized by hyperresponsiveness and inflammation of the airway with increased expression of inducible nitric oxide synthase (iNOS) and overproduction of nitric oxide (NO). Grape seed proanthocyanidin extract (GSPE) has been proved to have antioxidant, anti-inflammatory and other pharmacological effects.

Aims and objectives: The purpose of this study was to examine the role of GSPE on airway inflammation and hyperresponsiveness in a mouse model of allergic asthma.

Methods: BALB/c mice, sensitized and challenged with OVA, were intraperitoneally injected with GSPE. HE staining and PAS staining were used to observe airway inflammation in lung tissue and airway mucous secretion. The quantification of cytokines in bronchoalveolar lavage fluid (BALF) and total serum immunoglobulin E (IgE) were detected by ELISA. The protein expression of iNOS was evaluated by immunohistochemistry and Western Blot analysis.

Results: GSPE remarkably suppressed airway resistance, and reduced the total inflammatory cell and eosinophil counts in BALF Treatment with GSPE significantly enhanced interferon (IFN-γ) level and decreased interleukin (IL)-4 and IL-13 levels in BALF and total IgE levels in serum. GSPE attenuated allergen-induced lung eosinophil inflammation and mucus-producing goblet cells in the airway. The elevated iNOS expression observed in the OVA mice was significantly inhibited by GSPE.

Conclusions: GSPE decreases the progression of airway inflammation and hyperresponsiveness by downregulating the iNOS expression, promising to be a potential in the treatment of allergic asthma.

P973

The effects of bacilli Calmette Guerin-polysaccharide nucleic acid on nasal airway inflammation and resistance in allergic rhinitis mice

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Background: Lots of data can be found to approve that exposure to mycobacteria has the potential to suppress the development of allergic rhinitis or atopy. But the influence of bacilli Calmette Guerin-polysaccharide nucleic acid (BCG-PSN) especially on nasal airway inflammation and resistance (RNa) on mice, are poorly understood.

Conclusions: The results show that BCG-PSN treatment of patients with allergic rhinitis mice would become a molecular target for the treatment of patients with allergic asthma.
Objective: Investigate the effects of BCG-PSN on nasal airway inflammation and resistance in allergic rhinitis mice.

Method: Balb/c mice were sensitized by intraperitoneal injection of ovalbumin (OVA) saline, then challenged by intranasal administration under conscious to establish an allergic rhinitis model. The mice were intervened with BCG-PSN by intranasal administration (1, 5, 10 μg) before sensitization. A novel method of RQmax was applied to measure nasal function. Then the inflammation of nose was accessed by nasal tissues histology.

Result: In 3 interventions groups the RQmax had no statistical difference compared to rhinitis group. But compared to the normal group, the RQmax of expiration in 10 μg group and the RQmax of inspiration in 10 μg group had no statistical difference. The number of eosinophils (Eos) in 10 μg group was lower than rhinitis group as well as mucosal thickness.

Conclusion: BCG-PSN can inhibit nasal airway inflammation and decrease nasal airway resistance in allergic rhinitis mice.

102. Asthma: risk factors and comorbidities

P974 Evaluation of inhalant allergen-specific IgE in wheezing infants as predictor for persistent symptoms

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The aim of this study was to assess the IgE immune response in infants who were hospitalized for wheezing and follow-up during school age.

Subjects and methods: Thirty-eight children with a mean age of 8.5 months (2–22 months), who had been hospitalized with acute wheezing episodes, were included in the study. Total IgE and specific IgE for food and inhalant allergens were assessed by FEIA, Uni CAP.

The wheezing infants were divided into three clinical groups according to the number of previous wheezing episodes: first wheezes (n = 22), second wheeze (n = 9) and children with recurrent – three or more episodes of wheezing (n = 7). After five years the children were evaluated for asthma and allergy including t IgE and allergen-specific IgE.

Methods: BCG-PSN can inhibit nasal airway inflammation and decrease nasal airway resistance in allergic rhinitis mice.

P975 Analysis of the environmental risk factors in patients with bronchial asthma, allergic to moulds in second year observation

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Mold is a common yet significant allergen. Approximately 5% of people with allergies are subjected to allergic reactions of the respiratory tract which may be caused by mold. It seems that although mold frequently occurs in the outdoor environment, it often happens that indoor exposure must be taken into account in diagnostic procedure. To decrease the risk of mold allergy development or aggravation, indoor mold growth in patient’s closest environment should be prevented. In case of mold colonization at home, school or office, symptoms which supports its growth, should be found so as to identify it and remove as quickly as possible. From January 2009 to December 2010, 421 subjects were recruited from among outpatients visiting the Asthma Outpatients, Poland. Among them, in 166 patients positive mould allergy tests were obtained. These patients were presented with symptoms of bronchial asthma. All examined patients were subjected to interview concerning environmental factors such as mold allergens. For this purpose a questionnaire was used concerning demographic factors, living conditions, determination of the age of the building, presence of moisture in the place of living, and active or passive tobacco smoking environment. It seems that exposure to environmental factors such as damp flat, old housing plus tobacco smoking, especially in flats of large concentration, may all be favourable to the occurrence of environmental mould allergy and be the cause of the rise of allergy symptoms as well as invoking exacerbations.

P976 Food allergy as a risk factor for habitual snoring

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Background: It has been suggested that habitual snoring (HS) has adverse health outcomes in children and it’s an important indicator of many clinical conditions such as atopy, cough and rhinitis.

Aim of the study: To determine the prevalence of HS in a cohort of children with food allergy (FA) and its association with atopic state, and other clinical symptoms such as cough, and rhinitis.

Methods: Seventy-four children (mean age 11.0±2.0 years; 36 males) with a history of FA were selected. Atopic status was determined by a SPT to a panel of primary aeroallergens and food allergens. Parents-administered questionnaires were used to collected information on children’s snoring and possible symptoms associated. HS was defined as snoring three or more times per week.

Results: In our experience, children with FA show an higher prevalence of HS compared to Italian age-matched population (respectively 23% ± 4.9%: p <0.001) (Brunetti et al. Chest 2001, 120, 1930-1935). Furthermore among HS children, children with food allergy (FA) and its association with atopic state, and other clinical symptoms such as cough, and rhinitis.

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Peripheral airway obstruction is a predictive sign of early asthma

Takayaki Miyamoto, Hitoshi Kobayashi, Ateak Sato, Yu Usami, Yutaka Nakamura, Kohei Yamanuchi, Division of Pulmonary Medicine, Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan

Introduction: Diagnosis of early asthma is important to introduce early intervention. However, despite of many reports, it has not been established yet.

Objectives: To perform spirometry and Impulse Oscillometry System (IOS) on early asthmatics and compared the data with those of patients with chronic cough symptom (CC) and acute bronchitis (AB).

Methods: Patients who complained of chronic cough, wheeze and dyspnea, and had never been diagnosed as bronchial asthma (BA) before were recruited to the present study. After having their informed consent, we performed spirometry and IOS, and measured bronchial hyperresponsiveness (BHR). After several months, these patients were diagnosed as bronchial asthma, chronic cough including cough variant asthma and acute bronchitis by development of symptoms, hematological analysis and other findings.

Results: 169 patients (male: 113; 67.2%; age: 41.4 ± 14.4 years) were included. Mean±SEM, n=89) was significantly increased compared to CC (5.2±1.4, n=32) and AB (6.4±7.6, n=23). FEV1 of BA was not significantly decreased compared to CC. However, both%V50 and%V25 of BA were significantly decreased compared to those of CC (V50: BA vs CC; 49.7±25.9 vs 70.2±16.4, p<0.005, V525: BA vs CC; 58.1±29.0 vs 74.1±12.3, p<0.05).%R (5-25) measured by IOS was significantly higher in BA than in CC (BA vs CC; 151.7±6 vs 52±26).

Conclusions: Decreases of%V50 and%V25 and increase of%R (5-25) in IOS which indicated peripheral airway obstruction were detected in early asthmatics not in CC. These results suggested that peripheral airway obstruction may be a useful predictive sign of early asthma, which can be detected by spirometry.

BHR of BA (Dmin: 1.1±200s, n=89) was significantly decreased compared to CC (%V50: BA vs CC; 5.25.9 vs 70.2±16.4, p<0.005, V525: BA vs CC; 38.1±29.0 vs 54.1±12.3, p<0.05).%R (5-25) measured by IOS was significantly higher in BA than in CC/AB (BA vs CC/AB; 151.7±6 vs 52±26).

Conclusion: Presence of bronchoprovocation test positivity effect the development of allergic respiratory disease: 7 year follow-up study

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In this study, we aimed to investigate the relation between bronchoprovocation test positivity an development of allergic respiratory disease. The inclusion criteria to study were disease duration more than 1 year, no chronic urticaria, no history of long acting antihistaminic and corticosteroid usage in a month. The patients with asthma and pulmonary symptoms, diseases causing positive methacholine provocation test (MPT), contraindication to the MPT, and abnormal pulmonary function test were excluded. 156 patients with chronic urticaria were included to the study. There was 108 (69.2%) female and the mean age was 42.5±4.13,19 years. The duration of disease was 6.05±4.3,3 (1-25) years.

After physical examination, pulmonary function test and MPT were performed to the all patients with chronic urticaria. At the beginning, MPT positivity was detected in 41 (26.3%) patients. There was no significant difference between patients with MPT (p<0.05) and MPT-) according to demographic findings. Mean dose of MPT and total IgE level were 2.64±3.36 mg/ml and 123.3±124.3, respectively. In MPT (+) patients, rate of doctor diagnosed asthma and allergic rhinitis were 46.8%, 60.9% respectively and they were 18.2% and 25.2% respectively in MPT-) patients (p<0.05). Presence of allergic disease in family members did not influence the development of these allergic respiratory diseases. Also total IgE level at the beginning did not related with development of these disease.

As a result, bronchoprovocation test can be (+) in chronic urticaria patients without pulmonary symptoms and this positivity can be first sign of respiratory allergic disease that will develop in future.
P984

Patients with asthma and comorbid allergic rhinitis: Is optimal quality of life achievable in real life?
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Background: Asthma trials suggest that patients reaching total disease control have an optimal Health Related Quality of Life (HRQoL). Rhinitis is present in almost 80% of asthmatics and impacts asthma control and patient QoL.

Aims and objectives: We explored whether optimal HRQoL was reachable in a real-life setting, and evaluated the disease and patient related patterns associated to optimal HRQoL achievement.

Methods: Asthma and rhinitis HRQoL, illness perception, mood profiles, rhinitis symptoms and asthma control were assessed by means of validated tools in patients classified according to GINA and ARIA guidelines.

Results: Optimal HRQoL, identified by Rhodesma Global Summary (GS) score ≤20, was reached by 78/209 (37.32%). No association between clinical and demographic characteristics, with the exception of age, and optimal HRQoL achievement was found. Patients reaching an optimal HRQoL differed in disease perception and mood. Asthma control was significantly associated with optimal HRQoL. (χ²=49.599; p<0.001) and well-controlled and totally controlled patients significantly differed in achieving optimal HRQoL. (χ²=7.617; p<0.006).

Conclusion: While the majority of asthma patients did not reach optimal HRQoL, it is achievable, in real life, independently from disease severity. Failure to achieve optimal HRQoL was related to unsatisfactory disease control. Patients reaching optimal HRQoL differ from others in disease illness perception and mood. Therefore, therapeutic plans should be directed toward achieving the best possible clinical control of asthma and comorbid rhinitis, but also incorporate individualized elements according to patient-related characteristics.

P985

Nasal airway resistance and correlation with lower airway involvement in allergic rhinitis
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Background: Allergic rhinitis often precedes onset of asthma. Nasal airflow obstruction is measured by rhinomanometry.

Aims and objectives: Determining nasal airflow obstruction by active anterior rhinomanometry. Correlating nasal resistance with clinical severity of rhinitis and incidence of latent lower airway involvement.

Materials and methods: 32 patients with allergic rhinitis underwent active anterior rhinomanometry to determine nasal airflow obstruction. Nasal airflow challenge test was performed.

Results: 56% of patients with mild rhinitis and 94% with moderate-severe rhinitis significantly raised nasal airway resistance values. (χ²=0.3 Pa/sec) 0.05)

Conclusions: Clinical severity of allergic rhinitis correlated with nasal airway resistance values measured by active anterior rhinomanometry.

P986

Chronic rhino-sinusitis in severe asthma improves at high altitude
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Background: Severe asthma and chronic rhino-sinusitis often coexist (Meltzer, JACI 2004). Patients with severe asthma have shown to benefit from high altitude treatment (Rijssenbeek AJRCCM 2010). It is unknown whether chronic rhino-sinusitis also improves at high altitude.

Aim: To investigate the effect of high altitude treatment on symptoms of upper and lower airways disease in patients with severe asthma and rhino-sinusitis.

Method: 137 patients with severe asthma treated at the Dutch Asthmacenter Davos were included. In 65 patients, using nasal steroids, sino-nasal symptoms (SNOT scores), asthma control (ACQ), exhaled Nitric Oxide (FeNO), use of oral and nasal steroids were analysed, as well as the relationship between parameters of upper and lower airways. Parametric and non-parametric tests were used where appropriate.

Results: The improvement in SNOT-20 correlated significantly with the improvement in ACQ (R=0.527, p<0.005), the improvement in SNOT-20 and ACQ correlated significantly with improvement in FeNO (R=0.489, p<0.005), and decrease in FeNO (R=0.426, p<0.005).

Conclusions: A simultaneous improvement in upper and lower airways symptoms and oral steroid use occurs at high altitude in patients with severe asthma and chronic rhino-sinusitis.

Implications: These beneficial effects on upper airways disease underscore the anti-inflammatory and steroid-sparing effect of high altitude treatment in patients with severe asthma.

P987

The relationship of gastroesophageal reflux with asthma quality of life and asthma control test in asthmatic patients
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Aim: In this study we aimed to investigate the relationship of gastroesophageal reflux with Asthma Quality of Life (AQLQ) and Asthma Control Test (ACT) in asthmatic patients.

Method: Between September – October 2010, total 50 patients followed with a diagnosis of asthma at outpatient clinic of Cerrahpasa Medical School Chest Diseases department were enrolled in this study. Patients' reflux symptoms in last one month were irrogated by using “Reflux Symptom Index” that consisting of 9 questions and graded from 0 to 5 (0: none; 1: very little, 2: low, 3: moderate, 4: severe, 5: very severe). ACT and AQLQ questionnaires were filled. Statistical analysis was done by sing SPSS 15.0 software.

Results: 34 patients (68%) were female and 16 (32%) were male, mean age was 42±14. The number of patients suffering from reflux was 23 (46%). The statistically very significant negative correlation was found between gastroesophageal reflux and AQLQ (r=-0.551; p<0.005). Between the presence of gastroesophageal reflux and ACT, the statistically significant negative correlation was found (r=-0.314; p<0.05) (Table 1).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
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<tr>
<td>SNOT-20 score</td>
<td>2.4 (0.74)</td>
<td>1.6 (1.0) *</td>
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<tr>
<td>SNOT-rhin. score</td>
<td>2.2 (1.1)</td>
<td>1.7 (1.1) *</td>
</tr>
<tr>
<td>ACQ score</td>
<td>3.1 (1.1)</td>
<td>1.7 (1.1) *</td>
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<tr>
<td>FeNO (ppb)</td>
<td>25 (5-224)</td>
<td>16 (3-70) *</td>
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<tr>
<td>Oral steroid dose (mg/day)</td>
<td>5 (0-10)</td>
<td>0 (0-30) *</td>
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<tr>
<td>Nasal steroid dose (μg/day)</td>
<td>200 (75-1200)</td>
<td>200 (6-1200)</td>
</tr>
</tbody>
</table>

* p<0.05
Asthma severity and body mass index relationship

Emir Maden 1, Turgut Teke 1, Sebnem Yosunay 2, Durdu Mehneth Yavas 2, Mustafa Dinc 1, Rukiye Metiner 1, 1Pulmonary Medicine, Selcuk University Meram Medical Faculty, Konya, Turkey; 2Pulmonary Medicine, Byshehir State Hospital, Konya, Turkey

Obesity is considered as a risk factor for asthma; however the relationship between obesity and asthma control is being discussed. In this study we aimed to evaluate the relationship between obesity and disease severity in asthmatic patients. Asthma patients diagnosed in our clinic (453 patients) were enrolled to study. BMI (kg/m2) of the cases were analyzed. BMI was classified as low (BMI, <18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), and obesity (≥30 kg/m2). The patients were divided in to two groups; BMI >30 kg/m2 (obese) and BMI ≤ 30 kg/m2 (normal). The two groups were compared to age, sex, smoking history, comorbidities (gastroesophageal reflux, hypertension, diabetes mellitus, glaucoma, psychiatric disease, hipertirodi), allergy skin test positivity and pulmonary function test parameters by using statistical program SPSS 15.0 software.

Results: The mean age of the 169 patients was 39.5±17.1 years; 52% were male and 48% were women. The obese group included 31 patients. The two groups were compared. In the group with normal weight FEV1 and FVC values were significantly higher (p=0.05). In the obese group the proportion of women and men, presence of gastroesophageal reflux and the hypertension, the average age of patients were statistically significantly higher than in normal group (p<0.05). There was no statistically significant difference between the two groups in terms of smoking history, diabetes mellitus, glaucoma, psychiatric disease, hipertirodi, allergy skin test positivity FVC%, FEV1%, FEV/FVC% parameters (p>0.05).

Conclusion: The gastroesophageal reflux and hypertension comorbidities were more commonly seen in obese asthmatic than non obese asthmatics.

The effect of obesity or overweight on airway hyperresponsiveness and clinical features in patients with asthma

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Background: Obesity is a risk factor of asthma in general population but the effect of obesity on airway hyperresponsiveness (AHR) or airway inflammation in asthma is not clear. This study attempted to evaluate the effects of obesity on asthmatics in the aspects of symptoms, AHR and severity.

Methods: The 852 asthmatics who were diagnosed based on clinical symptoms and AHR confirmed by methacholine bronchial provocation test were enrolled from COREA adult asthma cohort. The intensity of AHR was assessed by provocative concentration of methacholine causing a 20% fall in FEV1 (PC20). BMI was classified into 4 categories, underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), and obesity (≥30 kg/m2).

Results: BMI was negatively correlated with FEV1 (L), FVC (L), and FEV1/FVC (%) in lung function test. The prevalence of wheezing was increased with the increase of BMI after adjustment for age, sex, smoking, medication history, and PC20 (<0.0001). AHI was higher in normal weight group than overweight group (P<0.001). The risk of moderate or severe AHR (PC20 ≤4 mg/ml) was increased when BMI increased after adjustment for age, sex, smoking, and medication history (P=0.035).

Conclusion: Obesity is a risk factor of asthma in general population but obesity in patients with asthma is negatively correlated with the intensity of AHR and not related with asthma severity. However obesity increases the prevalence of wheezing in asthmatics although obesity does not increase AHR.

The increased comorbidities in obese asthmatics

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Aim: Many studies have demonstrated an association between obesity and asthma, also the affects of obesity with airway inflammation were investigated. The aim of this study was to investigate the difference of age, sex, atopy, comorbid diseases and pulmonary function test parameters between obese and non obese asthmatics.

Method: The data files of 210 asthmatic patients who admitted to our outpatient clinic in 2010 were evaluated. 169 patients without atactic, with asthma control test over 20 and assessed BMI (body mass index) value enrolled in this study. The patients were divided in to two groups; BMI≥30 kg/m2 (obese) and BMI<30 kg/m2 (normal). The two groups were compared to age, gender, smoking history, comorbid diseases (gastroesophageal reflux, hypertension, diabetes mellitus, glaucoma, psychiatric disease, hipertirodi), allergy skin test positivity and pulmonary function test parameters by using statistical program SPSS 15.0 software.

Results: The mean age of the 169 patients was 39.5±17.1 years; 52% were male and 48% were women. The obese group included 31 patients. The two groups were compared. In the group with normal weight FEV1 and FVC values were significantly higher (p=0.05). In the obese group the proportion of women and men, presence of gastroesophageal reflux and the hypertension, the average age of patients were statistically significantly higher than in normal group (p<0.05). There was no statistically significant difference between the two groups in terms of smoking history, diabetes mellitus, glaucoma, psychiatric disease, hipertirodi, allergy skin test positivity FVC%, FEV1%, FEV/FVC% parameters (p>0.05).

Conclusion: The gastroesophageal reflux and hypertension comorbidities were more commonly seen in obese asthmatic than non obese asthmatics.

The role of inflammatory cells, adhesion molecules, intermediate filaments and chemokine receptors in the pathogenesis of nasal polyps

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Pathogenesis of nasal polyps is incompletely understood. This study investigates the role of inflammatory cells, adhesion molecules, intermediate filaments and chemokine receptors in development of nasal polyps. Totally, 35 patients were enrolled (Group 1, 10 patients with Samter syndrome; Group 2, 10 patients with diffuse polyps without signs of Samter syndrome; Group 3, 5 patients with solitary nasal polyps; Group 4, 10 controls). Expression of CD147, CD62E, CD4, CD8, CXCR4, CD147, CD90, CD104, BF45, vimentin, pancytokerin and MASA were determined. Expression of CD4, CD8 and CD104 were significantly higher in patients expressing vimentin in Group 1, Group 2 and Group 3 than in Group 4. Ratio of patients expressing vimentin in Group 1, Group 2 and Group 3 were significantly higher in all 3 groups than control group. Expression of CD147 in Group 3 and Group 4 was significantly higher than in Group 1 and Group 2. CD98 expression was higher in Group 1, Group 2 and Group 3 than in Group 4. Ratio of patients expressing CD98 antigen were significantly higher in all 3 groups than control group. Expression of CD147 in Group 3 and Group 4 was significantly higher than in Group 1 and Group 2. CD98 expression was higher in Group 1, Group 2 and Group 3 than in Group 4. Ratio of patients expressing CD98 antigen were significantly higher in all 3 groups than control group.
103. Respiratory epidemiology: genetics and modifiable risk factors

P993 European screening for α1-antitrypsin deficiency in subjects with lung disease Timon Greschko1, Helen Meters2, Bernard Budinger3, Gyorgy Losonczy4, Ludmilla Borsa5, Dalcius Vaiuciu6, Ivan Solovei7, Matjaz Flazer8, Marcela Vigdorovici9, Tatyana Martynenko9, Tetyana Pertseva10, Sandra Camprubi11, 1Department of Internal Medicine, Division for Pulmonary Diseases, Hospital of the University of Marburg, Marburg, Germany; 2Department of Pulmonology, District Dispensary for Pulmonary-Phthisis Diseases with Inpatient Hospital, Russe, Bulgaria; 3Department of Pulmonology, University Hospital for Lung Diseases Jandovance, Croatia; 4Department of Pulmonology, Semmelweis University, Budapest, Hungary; 5Department of Pulmonology, District Dispensary for Pulmonary-Phthisis Diseases with Inpatient Hospital, Russe, Bulgaria; 6Diagnostic Department of Internal Medicine, Vlahia University Hospital Sfantu Gheorghe Clinic, Vlahia, Romania; 7Department of Pulmonology and Physiology, National Institute for Tuberculosis, Lung Diseases and Thoracic Surgery, Hggy, Slovakia; 8Department of Pulmonology, District Hospital, Instituto Grifols, S.A., Barcelona, Spain; 9Department of Internal Medicine, Division for Pulmonary Diseases, Hospital of the University of Marburg, Marburg, Germany; 10Department of Pulmonology, University Hospital for Lung Diseases Jandovance, Croatia; 11Department of Pulmonology, Semmelweis University, Budapest, Hungary; 12Department of Pulmonology, Marius Nasta University Hospital Oradea, Oradea, Romania; 13Department of Pulmonology, Municipal Medical Institution City Hospital #5, Barnaul, Russian Federation; 14Department of Hospital Therapy, Dnepropetrovsk State Medical Academy, Dnepropetrovsk, Ukraine; 15Diagnostic Trials and Pharmacovigilance Department, Instituto Grifols, S.A., Barcelona, Spain

Introduction: Alpha1-antitrypsin deficiency (AATD) is a common hereditary disorder that predisposes to early-onset pulmonary embolism. Despite its prevalence, AATD is highly underdiagnosed. According to published guidelines for AATD, a diagnostic testing is greatly recommended in symptomatic adults with emphysema, COPD, or asthma with airflow obstruction incompletely reversible after aggressive bronchodilator treatment.

Aim: To investigate AATD presence in ten European countries targeting a cohort of symptomatic subjects.

Methods: Blood samples from adult subjects with lung disease were collected as dried blood spot (DBS). Detection testing algorithm consisted of 3 steps: first, all DBS specimens were analysed for α1-antitrypsin (AAT) levels by nephelometry; second, only samples with AAT levels below normal range (0.83 – 2.00 g/l) were genotyped for S- and Z-alleles by polymerase chain reaction; third DBS were phenotyped by isoelectric focusing in case of PS, PZ and non-S non-Z allele results.

Results: A total of 5396 subjects from Bulgaria, Croatia, Hungary, Latvia, Lithuania, Romania, Russia, Slovakia, Slovenia, and Ukraine were screened in 11 months. Seven hundred and eighty two (14.4%) had DBS AAT levels below the normal range. Among them, detection of S- and Z-alleles showed 16 PIZZ, 1 PISZ, 5 PSS, 38 PSZ, 79 PZ and 642 non-S non-Z variants. AAT genotyping of PIZ, PSS and non-S non-Z alleles revealed 1 PIZZrze, 38 PMZ, 78 PMZ, 579 PMIZ and 63 non allele. Detection rate of severe AATD in symptomatic subjects was 0.41%.

Conclusions: These data suggest a significant preventive approach in countries with a large number of symptomatic subjects but low awareness about this genetic condition.

In conclusion, inflammatory cells, adhesion molecules, intermediate filaments and chemokine receptors may play a role in pathogenesis of nasal polyps.

P994 Alpha1-antitrypsin deficiency in Italy: Analysis of the Italian registry disease

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Alpha1-antitrypsin Deficiency (AATD) is a rare hereditary disorder with a prevalence of about 1/5000 individuals in Italy. Deficient patients are at a higher risk to develop lung emphysema at an early age and liver cirrhosis. The low prevalence of AATD suggested the establishment of a registry with the aim to learn more details about the natural history and the quality of care of these patients. The Italian Registry of AATD was established in 1995. A total of 312 adult subjects with severe AATD were enrolled, namely 206 PIZZ, 48 PISZ, 3 PSS and 55 patients with, at least, one rare deficient allele (R). The frequency of 17.6% of PPRR is the highest so far recorded in national registries of AATD. Clinical data have been collected 253 were index-patients, mainly affected by lung and liver diseases (79% and 10%, respectively), and 55 were enrolled because of kinase with AATD patients. Mean age of enrollment was significantly higher (49.6 ± 14.4 years) than in non-index (43.5 ± 14.5 years). The mean interval between the onset of symptoms and the final diagnosis was 8 years for patients with lung diseases, and 13 years for liver diseases. Among index patients, most of them were former-smokers (63%). From 1999, 100 patients underwent augmentation therapy with purified AAT (Prolastin); they were mainly former-smokers (75%) with panlobular emphysema (34%). Interestingly, 10% of patients receiving augmentation therapy were non-index subjects. The data of the registry allow a detailed characterization of the natural course of the disease and the levels of the patient care, and confirm the usefulness of early detection of AATD.

P995 The polymorphisms of C-reactive protein gene modify the association between central obesity, asthma and lung function in Taiwan

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Background: High-sensitive CRP concentrations and obesity are proposed to cause asthma and impaired lung function, but little has been reported to date on the association between CRP gene and asthma.

Objective: Three tagSNPs polymorphisms for CRP gene were selected from HapMap data, and genotyping by using TaqMan allelic discrimination assay. We studied the association of polymorphism in CRP gene and their interactions with central obesity on asthma and lung function.

Method: A total of 814 asthmatic adults and controls were recruited in southern Taiwan. All subjects underwent questionnaire interviews, pulmonary function tests and genotyping. We detected three single nucleotide polymorphisms of CRP gene, and analyzed gene-obese interaction on the risk of asthma.

Results: We found that BMI and WIR were associated with hs-CRP concentrations. Although CRP SNPs alone and haplotypes were not associated with asthma risk, the association of asthma with central obesity, measured as the waist-to-hip ratio (WHR), seemed to be stronger in subjects who carries A/T heterozygote (p=0.042) in index (49.6 ± 14.4 years) than in non-index (43.5 ± 14.5 years). The mean interval between the onset of symptoms and the final diagnosis was 8 years for patients with lung diseases, and 13 years for liver diseases. Among index patients, most of them were former-smokers (63%). From 1999, 100 patients underwent augmentation therapy with purified AAT (Prolastin); they were mainly former-smokers (75%) with panlobular emphysema (34%). Interestingly, 10% of patients receiving augmentation therapy were non-index subjects. The data of the registry allow a detailed characterization of the natural course of the disease and the levels of the patient care, and confirm the usefulness of early detection of AATD.

P996 DNA and fatty acids oxidative stress in respiratory diseases: Preliminary results from the GEIRD study

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Among the determinants of respiratory diseases, emphasis has recently been placed on oxidative stress, but its role on the occurrence of the respiratory diseases is only partially known. The aim of this study is to investigate the oxidative stress levels in people with respiratory diseases and controls. 8-OhdG, a DNA oxidation product, and 8-oxoproline, a lipid oxidation product, were measured in spot-urine samples collected in the frame of Genes Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. Controls and cases of COPD, current asthma, past asthma, non-allergic rhinitis, allergic rhinitis and other respiratory conditions (n= 239, 19, 122, 70, 58, 45 and 76 respectively) were analysed to test differences in levels of urinary creatinine-corrected 8-OhdG and 8-oxoproline, using quantile regression models adjusting for age, gender, smoking habits, BMI and other potential confounders. Adjusted 8-OhdG median concentrations were significantly higher in allergic...
value for obesity and SOD GG genotype is 2.68 (95%CI, 1.30-5.55). Compared with non-obesity and SOD AG/GG genotype, we found that the AOR was significantly higher than the controls. The activities of SOD and CAT in new SOD Ala16Val and CAT C-262T and asthma. The WHR of asthmatic patients in our study, we did not find any significant association between the SOD gene Ala16Val and CAT gene C-262T.

Introduction: Smoking is a risk factor for COPD but little is known about whether this risk differs by genetic ancestry. The few prior studies rely on self-reported race/ethnicity.

Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of adults without clinical cardiovascular disease in the United States. Principal components (PCs) of ancestry were derived from genome-wide data (Affymetrix 6.0) in MESA. Variance was measured by AT/ERS guidelines. We tested the interaction of PCs with packyears of smoking on FEV1, stratified by gender and adjusted for age, height, weight, and smoking in women. PCs did not modify the relationship of packyears to FEV1 (p=0.86). In men, the relationship was modified by PCs (p=0.01), specifically PC2 (tracking Asian ancestry) was associated with lower FEV1 in all groups (p<0.001). In women, PCs did not modify the relationship of packyears to FEV1 (p=0.086). In men, the relationship was modified by PCs (p=0.001), specifically PC2 (tracking Asian ancestry) was associated with less of a decrement in FEV1 per packyears smoking (p=0.001).

Conclusion: Variation between European and African ancestry did not modify the relationship between smoking and lung function in either gender, but this relationship may be modified by Asian ancestry in men.

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The associations between the adult asthma, central obesity and gene polymorphisms and activities of superoxide dismutase and catalase

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Background: Adult asthma is caused by interaction effects of genetic and environmental factors. Previous studies have indicated that obesity may increase the risk of asthma but not for central obesity. This would enable us to further investigate the mechanism of defective antioxidant enzymes for asthma pathogenesis.

Conclusion: The activities of SOD and CAT are significantly related to adult asthma but not for central obesity. This would enable us to further investigate the mechanism of defective antioxidant enzymes for asthma pathogenesis.

P1000

Birth mode and gut microbiota influence the risk of allergies and asthma – The KOALA birth cohort study

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Background: Gut microbiota (GM) composition and birth mode have been linked to allergies. However, results are inconsistent and the hypothesized intermediate role of GM in the association between birth mode and allergies has not been studied yet.

Aim: To study the relationship between GM composition, birth mode and allergic phenotypes.

Methods: The KOALA-study includes data on birth mode and on allergic symptoms from birth until age 6 years. Faecal samples were collected at age 1 month (n1=176) to determine GM composition using 16S rRNA. Blood samples were collected at ages 1, 2, and 6 years to determine specific IgE levels against common allergens.

Results: Infants born by caesarean (C-)section had lower numbers of bacteroides C. difficile prevalence was highest in infants born by C-section (42%), followed by infants born vaginally in the hospital (26%) and at home (19%). Colonisation by C.difficile was associated with an increased risk of eczema, wheeze and sensitisation throughout the first 6 years of life and with asthma (OR: 2.02, 95%CI: 1.15-3.56) at 6 years. Regarding mode and place of delivery, only children with atopic parents had an increased risk of asthma (2.06, 1.27-3.35) and sensitisation to food allergens (1.91, 1.29-2.84) when they had been vaginally delivered in hospital, when compared to vaginal delivery at home. C-section also increased the risk of sensitisation to food allergens (2.16, 1.21-3.86) compared to infants delivered at home.

Conclusion: Birth mode strongly influences the GM composition and both are associated with allergic manifestations, including asthma. More extensive microbial profiling is needed to examine whether C.difficile reflects other shifts in GM.
P1001
Patterson, sensitization in early childhood in farming environment: A French part of the PASTURE/FOREALL European birth cohort study
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Background: Cross sectional studies have repeatedly shown that children growing up on a farm had a significantly lower prevalence of atopic sensitization measured by specific IgE (IgEs) in serum but very little is known regarding sensitization tested by skin prick-tests (SPT).

Objective: To compare SPT-tested sensitization during the first 4.5 years of life in children born and living on dairy farms (F) and in children of families from the same rural area, but not born and not living on farms (non-F).

Methods: 168 children at 1 yr (49% F; 49% boys) and 155 at 4.5 yrs (52% F; 52% boys) were tested by SPT using a battery of 11 (1 yr) and 16 (4.5 yrs) age- and area-adepted antigens. Correspondent serum specific IgE were measured at both ages.

Results: Prevalence of at least one positive SPT was of 8.5% (1 yr), 9.6% (4.5 yrs) in F and 11.6% (1 yr), 19.5% (4.5 yrs) in non-F groups (p=0.05). In the whole population, positive SPT were mainly against food allergens at 1 yr (13/17, 12 for egg antigen) and against Aeroallergens in 4.5 yrs (24/26, 15 for seasonal antigens). At 1 yr, 17% of girls had positive SPT, versus 5.5% of boys, compared with 4.5 yrs (10.7% vs 17.5%). No relationship between IgE and SPT-tested sensitization was observed at 1 yr. Such a relationship was demonstrated at 4.5 yrs considering all antigens as well as categories (food, seasonal, perennial) but not for each single antigen.

Conclusions: The prevalence of positive skin prick tests is significantly lower in children growing up on a dairy farm than in their rural peers. At one year, there is no correlation between SPT and IgE-tested sensitizations.

P1002
Air pollution and development of respiratory system: A 19-year cohort study among children in Franche-Comté, France
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Background: At follow-up while 47.1% of the adult group had severe nasal obstruction (flow <20%) at 1 yr and 17% of girls had positive SPT, versus 3.5% of boys, compared with 4.5 yrs (24/26, 15 for seasonal antigens). At 1 yr, 17% of girls had positive SPT, versus 5.5% of boys, compared with 4.5 yrs (10.7% vs 17.5%). No relationship between IgE and SPT-tested sensitization was observed at 1 yr. Such a relationship was demonstrated at 4.5 yrs considering all antigens as well as categories (food, seasonal, perennial) but not for each single antigen.

Objective: To examine the combined effect of weather, pollution and topography on the development of respiratory symptoms and function in schoolchildren

Methods: For one year, 52 subjects recorded daily respiratory symptoms. These correlations demonstrate a combined effect of certain weather conditions on acute exacerbations, especially those which result in airborne water droplets formation. The deleterious influence of pollution is also confirmed. Particles can serve as nuclei for airborne water droplets formation and an increased retention of particles and pollutants under these weather conditions is suggested.

Results: Statistically significant (p<0.05) relationships were recorded between altitude and exacerbations frequency (r=-0.33 to -0.44), relative humidity (r=0.19 to 0.43), temperature (r=-0.08 to -0.58), dew point (r=0.13 to -0.42), and the difference between temperature and dew point (r=0.19 to -0.46) showed predominately statistically significant relationships with symptoms. Particulates showed some of the strongest correlations with symptoms (r=0.11 to 0.44). Generally, an adjustment of data for infectious exacerbations led only to minor changes in the results.

Conclusion: Our study provides for the first time evidence of increased respiratory symptoms in lower altitude areas of river valleys. The correlation results demonstrate a combined effect of certain weather conditions on acute exacerbations, especially those which result in airborne water droplets formation. The deleterious influence of pollution is also confirmed. Particles can serve as nuclei for airborne water droplets formation and an increased retention of particles and pollutants under these weather conditions is suggested.

P1004
Spatial distribution of COPD in a rural population in India using geographic information system (GIS)
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GIS mapping is a useful tool to study the spatial distribution of diseases and examine their association with geographic risk factors. We used GIS to determine spatial distribution of COPD in 22 rural villages spread across an area of 232 km², and study the association between proximity to highways and prevalence of COPD.

Methods: 3,952 randomly selected individuals were administered a respiratory health questionnaire and underwent pre and post bronchodilator spirometry (forced expiratory volume in one second) according to the ATS/ERS standards. COPD was defined as post-bronchodilator FEV1/VC<0.7. Each individual’s residence was mapped using Global Positioning system (Garmin eTrex, USA). Spatial distribution of all individuals and the association between proximity to highway and prevalence of COPD were performed using ArcGIS software version 9.3, USA.

Results: A significant cluster of COPD subjects were found residing <500m from the highway (Moran’s Index = 0.07; p<0.01). 90% of individuals residing <500m from the highway used liquified petroleum gas for cooking and in this population a strong positive correlation was found between proximity to highways and COPD prevalence (OR 2.39; 95% CI 1.04-5.54). Individuals who resided >500m from the highway had a higher prevalence of COPD and this was strongly associated with the use of biomass fuel (OR: 1.46; CI: 1.06-2.01; p<0.01).

Conclusion: Residing <500m from the highway was strongly and positively associated with COPD. The prevalence of COPD was three-fold higher amongst those living >500m from the highway and this was significantly associated with the use of biomass fuel.

P1005
Effect of urban vehicular traffic pollution on respiratory symptoms and pulmonary function in schoolchildren
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Our aim was to evaluate the relationship between pollution from urban traffic on respiratory symptoms and function in adolescents. In 2005-2006 we performed a survey on 2,150 schoolchildren (10-17 yrs) from 16 junior high schools in the city of Palermo, Italy. Subjects fulfilled an ISAAC questionnaire and underwent spirometry and skin tests. The geographic location of each residence was geo-coded by Geographic Information System. A vehicular traffic model computed the daily average traffic of 2,561 road segments in the city and was used for estimating the amount of traffic close to each dwelling. We identified 3 areas with progressively increasing traffic: A (in the West side close to the hills around the city - 14.8% of subjects); B (central - 53.3%); and C (the outskirts in the North and South of Area B - 31.5%). Prevalence of respiratory symptoms was: wheeze ever (WE), 22.1% in Area A, 22.1% in Area B, and 23.3% in Area C (p=0.02); asthma ever (AE), 8.1%, 12.4%, and 13.0%, respectively (p=0.068); impaired lung function (ILF) was present in 1.7% of subjects, in 4.1%, and in 5.2%, respectively (p=0.037). In a logistic regression model, Odds ratios (OR) with 95% confidence intervals (CI) were calculated with Area A as reference and corrected for confounders: Area B was a significant risk factor for WE (OR 1.66, IC 1.17-2.36), AE (OR 1.83, IC 1.15-2.91), and ILF (OR 2.71, IC 1.06-6.89). The corresponding OR for Area C were 1.66 (IC 1.16-2.40), 1.72 (IC 1.06-2.80), and 3.42 (IC 1.32-8.84), respectively. Our results point out that children exposed to increased levels of urban vehicular traffic near the house of residence are at higher risk for asthma and impaired lung function. 

177s
Long-term effect of urban air pollution on lung function
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Background: Long-term effects of air pollution on lung function remain uncertain particularly for adults.

Aims: To investigate the association between exposure to nitrogen dioxide (NO2) – used as a marker for local traffic-related pollution – and particulate matter <10 microns (PM10) in the urban area of Grenoble (France) and lung function in adults.

Methods: Lung function parameters (FEV1, FVC, %FEV1/FVC measured predicted) were assessed using the Stanojevic equations were assessed between 2001-2007 for 450 adults living in Grenoble (120 asthmatics and 330 non asthmatics), in the frame of the INTERMONITOR study and the NO2 database (1999-2003).

Results: Measurements (μg/m³) were 34 (IQR 31-38) for NO2 and 31 (IQR 29-33) for PM10. In non asthmatics, for a 10 μg/m³ increase in NO2 and PM10, FVC% predicted decreased by 3.7 (p=0.01) and 11.7 (p=0.03) and FEV1% predicted by 3.3 (p=0.02) and 9.0 (p=0.07) respectively. Similar but not significant negative trends were observed in asthmatics.

Conclusion: Results suggest negative associations of home outdoor NO2 and PM10 with lung function in non asthmatics.

Grant: region Rhône-Alpes (CIBLE).

Influences of smoking habits on annual change in FEV1 - A 12-year follow-up study
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Background: The rate of forced expiratory volume in 1 second (FEV1) decline is a marker of chronic obstructive pulmonary disease risk. To date, limited longitudinal data exist on airflow obstruction (COPD) and FEV1 decline in Japan.

Aims and objectives: The aim of this study was to investigate the rate of FEV1 decline by smoking habits over a 12-year periods in Japanese males.

Methods: The study included 913 male subjects, aged 30-76 years at baseline, whose lung function tests at a medical check-up in 1994 (baseline), 1999, and 2006. The study group consisted of 263 persistent never smokers, 296 early quitters (those who stopped smoking between 1994 and 2006), 117 late quitters (those who stopped smoking between 1999 and 2006), and 237 persistent smokers without airflow obstruction at baseline. Airflow obstruction (AO) was defined as FEV1/FVC<0.7 and 5th percentile lower limit of normal (FEV1/FVC<0.7). LOCP was defined as FEV1/FVC<0.7 and 5th percentile lower limit of normal (FEV1/FVC<0.7).

Results: Mean annual decline in FEV1 over a 12-years period was -35.0 ml/yr in persistent never smokers, -37.9 ml/yr in early quitters, -40.7 ml/yr in late quitters, and -44.8 ml/yr in persistent smokers. Mean annual decline in FEV1 over a 12- year periods defined using the fixed criteria and the LLN criteria were -34.6 ml/yr, -34.3 ml/yr in persistent never smokers without AO, -42.3 ml/yr, -42.3 ml/yr in persistent smokers without AO, -60.3 ml/yr, and -56.7 ml/yr in persistent smokers with AO, respectively.

Conclusions: Persistent smokers with AO had a significant reduced FEV1 decline compared with those in persistent never smokers and current smokers without AO. Our study confirmed that early cessation of smoking may reduce the FEV1 decline and prevent the development of AO among smokers.

Risk factors for obstructive lung function in morbidly obese patients
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Background: Morbidly obese patients are not only at risk for asthma but also for pulmonary complications related to bariatric surgery.

Aim of the study: To calculate a risk score for obstructive lung function in morbidly obese patients as pre-surgical screening tool before bariatric surgery, and relating pulmonary complications to this score.

Methods: 39 of the 342 patients (11.4%) had an obstructive lung function. A history of asthma (adj OR 3.2; 95% CI 1.4-7.5), <5 pack years (adj OR 2.8; 95% CI 1.2-6.3) and abdominal circumference >120cm (adj OR 7.0; 95% CI 1.6-31.0) were associated with an obstructive lung function (multiple logistic regression). The risk of obstructive lung function was calculated (1, 1 and 2 points respectively).

P1006
Reduced body mass index is associated with the presence of airflow obstruction in a rural Indian setting
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Background: Respiratory conditions remain a significant source of morbidity globally. We wished to understand factors associated with the development of airflow obstruction (AO) within a rural Indian setting. We hypothesised that being significantly underweight (BMI less than 18.5) could be linked to the development of AO (FEV1/FVC less than 0.7).

Methodology: Patients greater than 35 years old attending a primary care outpatient clinic at Chengal, West Bengal, India underwent: 1. A structured questionnaire 2. Measurement of BMI 3. Spirometry (analysed by a Respiratory Clinical Physiologist for Global Initiative for Obstructive Lung Disease). Results: 416 patients (mean age 51 years; 47% male; 62% never smokers) completed the study; spirometry deemed valid for analysis in 286 (69%); 47 (16%) of all subjects were noted to exhibit AO; GOLD stage 1 (15%); GOLD stage 2 (49%); GOLD stage 3 (26%); GOLD stage 4 (10%). Never smokers comprised 43% (2047) of all AFO cases. On logistic regression, factors associated with AFO were: Increasing age (95% CI 0.004-0.011; p=0.005), smoking status (95% CI 0.07-0.17; p=0.006), male gender (95% CI 0.19-0.47; p=0.012), reduced BMI (95% CI 0.19-0.65; p=0.02) and occupation (95% CI 0.12-0.84; p=0.08). Mean BMI was significantly lower in the 47 patients with AFO (20.1 ± 21.6; p=0.02).

Conclusion: Our study suggests that being underweight is associated with the presence of AFO in a rural Indian setting.
prescribed in 35 patients, of whom 34% (97%) had a risk-score of ≥2 (p<0.000). Only 5 pulmonary complications occurred, however all pulmonary complications were in ≥2 group (p=0.225).

Conclusion: Abdominal circumference is a better predictor than BMI for obstructive lung function in morbidly obese patients undergoing bariatric surgery. Although the incidence of pulmonary complications after bariatric surgery is low, pre-surgical risk factor analysis could identify patients at risk for obstructive lung function and pulmonary complications.

P1011
Associations of different serum 25(OH)D levels to parameters of respiratory health in COPD patients
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Recent studies show a high prevalence of vitamin D deficiency in COPD patients. Optimal vitamin D levels may differ for different physiological processes. There is no current consensus on the optimal level for respiratory health and lung function.

Methods: Serum 25(OH)D in 426 COPD patients. GOLD stage II-IV, aged 40-76, from the Bergen COPD Cohort study, were determined by liquid chromatography double mass spectrometry. Examinated explanatory variables were sex, age, body mass index (BMI), smoking habits, FEV1, exacerbation frequency, PaO2, respiratory symptoms, use of inhaled steroids, CRP, total white blood (WBC) count and seasonality. Vitamin D levels were categorised into 5 groups (A,B,C,D,E): A: <10ng/ml; B: 10-20ng/ml; C: 20-30ng/ml; D: 30-40ng/ml; and E: 40-52ng/ml. Associations were tested with chi-square and Kruskal Wallis.

Results: The prevalence of subjects in vitamin D categories, A to E, were 6.8%, 26.5%, 33.1%, 27.0%, and 6.6% respectively.

The percentage of daily smokers in group A through E were: 58.6%, 53.1%, 39.7%, 38.8%, and 58.6% (p=0.046).

Mean FEV1 was 43%, 43%, 51%, 51%, and 56% in group A through E (p<0.001).

Conclusion: Vitamin D deficiency (<20ng/ml) was common in COPD patients and significantly related to important disease phenotypes, but the critical cutoff level of vitamin D varied between the different respiratory health variables.

P1012
Microbial evaluation of proton pump inhibitors and the risk of pneumonia
Sabine Meijvis1, Marie Claire Cornips 2, Paul Voorn3, Patrick Souverein2

Recent studies suggested a possible risk of community-acquired pneumonia in patients using proton pump inhibitors (PPIs). This study aimed to identify colonizing gastrointestinal bacteria and the risk of pneumonia in patients using different PPIs.

Methods: This was a case-control study with 609 patients using PPIs from general practitioners. Risk factors for pneumonia were evaluated using logistic regression.

Results: Recent initiation of PPI treatment (<30 days) was associated with an increased risk of pneumonia (OR 2.2; 95% CI 1.0-4.6). The risk of pneumonia was not significantly different between different PPIs.

Conclusion: Recent initiation of PPI treatment may increase the risk of pneumonia. Further studies are needed to confirm these findings.

P1013
Late-breaking abstract: A prospective study of central obesity, overall obesity and incident asthma in adults
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Introduction: Measures of body mass index (BMI) and waist circumference (WC) define overall obesity and central obesity respectively. While high BMI has been established as a risk factor for asthma in adults, WC has seldom been investigated.

Aims and objectives: We conducted a prospective cohort study to investigate the individual and combined effect of central obesity and overall obesity on adult incident asthma.

Methods: A total of 23,245 adults without asthma, 19-55 years of age from the second Norwegian Nord-Trøndelag Health Study (HUNT), were followed for 11 years. WC and BMI were measured and categorised as central obesity (WC ≥88cm in women and ≥102cm in men) and overall obesity (BMI ≥30.0 kg/m²). Asthma incidence was self-reported during the follow-up. Odds ratios (OR) were calculated by logistic regression models adjusted for age, smoking status, education, family history, physical activity, social benefit, economical difficulty and sex.

Results: Of the 23,245 adults in the analysis, 12% (n=2,792) were overall obese, 13.6% (n=3,170) were centrally obese at baseline and 3.5% (n=818) had asthma during the 11-year follow-up. Central obesity in the absence of overall obesity was significantly associated with incident asthma (OR 1.44, 95% confidence interval (CI) 1.09-1.91). The OR for overall obesity in the absence of central obesity was 1.38 (95% CI 0.96-2.00), similar to central obesity alone. Central obesity combined with overall obesity (OR 1.81, 95% CI 1.48-2.23) is compatible with an additive effect of BMI and WC on asthma.

Conclusion: Central obesity and overall obesity seem to have an individual effect on incident asthma in adults and an additive effect when in combination.

P1014
Trends in co-morbidity in oxygen-dependent COPD
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In recent decades, mortality from non-respiratory diseases has increased in patients on long-term oxygen therapy (LTOT) for COPD (Ekstrom, M.P. et al. AJRCCM. Epub 2011 Jan 7). This study tests the hypothesis that co-morbidity has increased over time in oxygen-dependent COPD.

Material and methods: Patients starting LTOT for COPD between 1 January 1992 and 31 December 2008 in the national Swedish Oxygen Register were included. All registered diagnoses within five years prior to initiating LTOT were collected retrospectively from the Swedish Hospital Discharge Register, which include about 99% of all public hospitalizations in Sweden. Odds ratios (ORs) for diagnosis entities per calendar year were estimated using logistic regression adjusted for age, sex, PO2 breathing air, FEV1, and smoking history.

Results: 6147 patients (55% women) with a mean age 71.6 ± 8.4 years were included in the analysis. Adjusted odds ratios per calendar year (OR; 95% confidence interval; P-value) increased for anaemia (1.07; 1.04-1.10; P<0.001), diabetes mellitus (1.04; 1.02-1.06; P<0.001), hypertension (1.14; 1.11-1.16; P<0.001), ischecmic heart disease (1.05; 1.04-1.07; P<0.001), pulmonary embolism (1.17; 1.12-1.23; P<0.001) and for renal failure (1.20; 1.14-1.26; P<0.001). There was no time-trend for cerebrovascular disease (P=0.141) or cancer (P=0.062).

Conclusion: Co-morbidity has increased over time, which could contribute to the increased mortality from non-respiratory diseases in oxygen-dependent COPD.

P1015
Coexisting cardiovascular diseases increase the risk of exacerbations in patients with COPD
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Background: Few studies published prediction models with exacerbation of COPD as the endpoint, and the prognostic value of coexisting cardiovascular diseases has never been evaluated adequately.

179s
Purpose: To develop a prediction model for exacerbation of COPD.

Methods: Data from an existing cohort of 244 patients with COPD according to the GOLD criteria were used, with a follow-up of 4.2 (SD 1.2) years. The initial assessment was between 2001 and 2003. Exacerbation of COPD was defined as a period of worsening of COPD symptoms necessitating boosts of prednisolone therapy. Univariable and multivariable logistic regression analysis was used to construct a final, reduced prediction model. After bootstrapping, c-statistics were used to estimate the ability of the model to discriminate between patients who suffered from an exacerbation and whom not.

Results: In total, 115 (47.1%) patients experienced at least one exacerbation and more than half (57.4%) of the patients had ≥ 2 exacerbations during the follow-up. The final reduced model included body mass index, FEV1 (as predictor), smoking history, systemic steroid use in the year before initial assessment, use of corticosteroid inhalers, a history of stroke/TIA, and a history of ischaemic heart disease. The c-statistic after bootstrapping was 0.81 (95%CI 0.76 – 0.86).

Conclusions: Variables related to severity of pulmonary obstruction, smoking history, but also a history of cardiovascular diseases were independent predictors of an exacerbation of COPD. More attention should be paid to unmask coexisting cardiovascular disease, because adequate treatment of these diseases could reduce exacerbations, but probably also mortality in patients with COPD.

P1018
Fibrinogen and all-cause mortality in a nationally representative US cohort
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Background: We aimed to study the association of lung function, fibrinogen and mortality.

Methods: We analyzed data from 8201 adults aged =25 years from the National Health and Nutritional Examination Survey (NHANES III). Hazard ratios were calculated to determine the risk of dying (all cause mortality) due to elevated fibrinogen values defined > 400 mg/dL (the top decile) and the interaction with lung function (determined using modified GOLD staging) and adjusted for age, sex, race-ethnicity, smoking, cardiac disease and diabetes.

Results: 3198 subjects (weighted%) 28 died during the follow-up of up to 18 years. The predictors of mortality are shown in the table (normal lung function with a fibrinogen level =< 400 mg/dL is the referent group for all the lung function categories).

Predictors of mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Fibrinogen &gt;400</td>
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</tr>
<tr>
<td>GOLD 3 or 4</td>
<td>5.4 (1.9, 9.5)</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>2.7 (2.0, 3.5)</td>
</tr>
<tr>
<td>GOLD 1</td>
<td>1.7 (1.1, 2.5)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.7 (1.3, 2.1)</td>
</tr>
<tr>
<td>Restricted</td>
<td>2.7 (1.9, 3.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.7 (1.3, 2.3)</td>
</tr>
<tr>
<td>Baseline Fibrinogen &lt;400</td>
<td></td>
</tr>
<tr>
<td>GOLD 3 or 4</td>
<td>3.6 (2.7, 4.9)</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>1.9 (1.6, 2.3)</td>
</tr>
<tr>
<td>GOLD 1</td>
<td>1.2 (1.0, 1.5)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.4 (1.2, 1.7)</td>
</tr>
<tr>
<td>Restricted</td>
<td>2.0 (1.7, 2.4)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.1 (1.0, 1.1)</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td>Black</td>
<td>1.3 (1.1, 1.5)</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>0.9 (0.8, 1.1)</td>
</tr>
<tr>
<td>Other</td>
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</tr>
<tr>
<td>Age</td>
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<tr>
<td>≥70</td>
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<tr>
<td>Smoking</td>
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</tr>
<tr>
<td>Former</td>
<td>1.2 (1.0, 1.4)</td>
</tr>
<tr>
<td>Current</td>
<td>1.9 (1.7, 2.2)</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>1.6 (1.4, 1.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>1.6 (1.4, 1.8)</td>
</tr>
</tbody>
</table>

Conclusion: Elevated fibrinogen values are important predictors of death and add to the predictive ability of impaired lung function to predict mortality.

P1019
COPD prevalence in chronic heart failure
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Introduction: COPD frequently coexists with chronic heart failure (CHF) leading to impaired prognoses as well as diagnostic and therapeutic challenges. However, lung functional data on COPD prevalence in CHF are scarce and COPD remains to be widely undiagnosed or misdiagnosed. The aim of this study was to determine COPD prevalence in CHF.

Methods: In this cross-sectional study spirometry was performed in 220 CHF patients (78.2% male, median age 71 years [IQR 63-77] with left ventricular dysfunction history, systemic steroid use in the year before initial assessment, use of ACE inhibitors, peripheral edema, blood pressure, tachycardia, PaCO2, creatinine, neutrophil count, NT-proBNP, and infiltrate on chest radiograph. In a multivariable model, patient age, history of hypertension, tachycardia, creatinine, neutrophil count >11.5 x10^9/L, and NT-proBNP remained significantly associated (p<0.05) with hs-cTnT.

Conclusion: Multiple variables, including those reflecting heart failure, renal dys- function, and inflammation are predictive of hs-cTnT during AECOPD, suggesting that the mechanisms underlying hs-cTnT elevation are multifactorial.
Background: Several studies have shown that low lung function (even within normal limits) as well as respiratory symptoms are associated with increased cardiovascular mortality. In a case referent study we have compared sputum from patients hospitalised for acute myocardial infarction (AMI) with sputum from a random sample in the general population. The objective was to investigate the association between inflammatory cells in the airways and AMI.

Methods: The cases (N=58, mean age 58 years) had a confirmed diagnosis of AMI and performed induced sputum within 96 hours after the onset of chest pain. The referents (N=120) were selected by random sampling from the hospital’s catchment area. Subjects aged 40–74 years (mean age 55 years) were invited to participate. Results: Only six patients (10%) were females and 27 patients (47%) were current smokers. The corresponding prevalence of COPD was 5% (49%) and 27% (23%), respectively. The total number (mean SD of sputum cells was 3.9 x 10^6/mL (4.2) and macrophage count was 1.10 x 10^6/mL (1.2) among cases, and 3.1 x 10^6/mL (2.8) (p=0.12) and 0.72 x 10^6/mL (0.69) (p=0.011) among referents. The difference in total macrophage count between the cases and the references increased with declining cholesterol (p=0.028). There was also a negative association with increasing age, systolic blood pressure, and current smoking, although not significant. Conclusion: AMI is associated with a high macrophage count in induced sputum from patients with a low cardiovascular risk profile, suggesting multifocal inflammatory activity.

P1021
High blood pressure, antihypertensive medication and lung function in a general adult population
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Background: Several studies have shown that high blood pressure as well as antihypertensive treatment are associated with reduced lung function in a general adult population. Furthermore, we speculate that the negative effect of antihypertensive medication on lung function is mainly attributable to beta-blockers.

Conclusion: Our analysis indicates that both high blood pressure and antihypertensive treatment are associated with reduced lung function in a general adult population. Furthermore, we speculate that the negative effect of antihypertensive medication on lung function is mainly attributable to beta-blockers.

P1022
Prevalence of pulmonary arterial hypertension and right ventricular dysfunction in COPD patients in the Kirov region of Russia
Julia Chuyasova, Vasily Pryanov, Elena Popova, Division of Respiratory Diseases, Kirov State Medical Academy, Kirov, Russian Federation

Purpose: To estimate the prevalence of pulmonary artery hypertension (PAH) and right ventricular (RV) dysfunction in COPD patients in the Kirov region of Russia.

Material and methods: 1088 COPD patients (mean age 55±14 years, 97% men and 3% women) were studied. All the patients underwent physical examination, laboratory investigations and transthoracic echocardiography. RV end-diastolic diameter, RV wall thickness and right atrium (RA) area were measured. The systolic pulmonary arterial pressure (PAP) was measured by pulsed Doppler (systolic PAP = tricuspid regurgitation pressure gradient + estimated RA pressure). RA pressure was estimated based on the diameter and respiratory variation of the inferior vena cava. Mean PAP was calculated with formula: mean PAP = 0.61 x systolic pressure + 2 mm Hg. Global RV systolic function was estimated using RV myocardial performance index and RV fractional area change. RV diastolic function was assessed using tricuspid e/a ratio and E/E’ ratio.

Results: PAH (systolic PAP > 37 mmHg and mean PAP > 25 mmHg) was detected in 40.3% of cases (438 patients). Right ventricular (RV) remodeling and dysfunction were revealed in all COPD patients with PAH. Diastolic RV dysfunction was detected in 100% and systolic RV dysfunction in 12.8% of those cases. Conclusion: Our study confirmed high prevalence of PAH and RV dysfunction in COPD patients in the Kirov region of Russia. Prognosis of these patients is characterized by an increased risk of death. Physicians should detect PAH in COPD patients as early as possible and start treatment for prevention complications.

P1023
Prevalence of comorbidities in patients with COPD in south-Spain
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Objective: The prevalence of comorbidities in COPD is variable according to different publications. Our objective was to analyze the prevalence of comorbidities in stable COPD patients in our area, and its relation to other parameters.

Material and methods: Concurrent multicenter prospective study that included stable COPD patients from 6 hospitals at the South of Spain. We obtained demographic, epidemiologic and pulmonary function test variables, Charlson and Deyo/IRE index, British Medical Research Council (BMRC) Dyspnea scale, London Chest Activity of Daily Living Scale (LCADL), Hospital anxiety and depression scale (HAD) and St George’s respiratory questionnaire (SGRQ).

Results: We studied 164 patients (83.5% males), with a mean age of 65.7 years and mean FEV1 of 49.7%. According to GOLD classification, 4.9% were in Stage I, 38.4% in Stage II, 45.1% in Stage III and 11.6% in Stage IV. The prevalence of cardiovascular disease or diabetes mellitus was 6.1%, peripheral vascular disease 8.5%, isquemic stroke 4.9%, ulcer disease 7.9%, diabetes 12.8%, neoplasms 11%, hepatic disease 10.4% and renal disease 2.4%. Using the HAD scale 14% of the patients showed anxiety symptoms, and 15.2% depression symptoms. 30% of patients have 1 comorbidity, 16.6% have 2 comorbidities and 3.7% have 3 or more.

Conclusions: The prevalence of comorbidities didn’t correlate with the severity of COPD. There was statistical correlation between Charlson index and hospital admissions due to COPD exacerbation.

P1024
The evaluation of systemic inflammation in COPD patients comorbidized with cardiovascular diseases or diabetes mellitus
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Background: COPD is one of so-called life-style related diseases and reported to show systemic inflammation, due to strong relationship to long-time tobacco smoking. Therefore, COPD patients often have a variety of comorbid diseases, in
cladding cardiovascular diseases (CVD), diabetes mellitus (DM), and other systemic diseases.

Purpose: To investigate smoking status and frequency of comorbid COPD among the patients with CVD, DM, or both, who had smoking history (≥ 10 pack-years), and also to investigate how CVD, DM or COPD is associated with systemic inflammation, oxidative stress and clinical disorders.

Method: Totally 83 patients, over 40 years with history of cigarette smoking, were recruited for this study. All the participants were examined for pulmonary function test with bronchodilator, urine 8-OHdG/Creatinine, plasma levels for TNF-α, hs-CRP and pentoxifylline as predictors of airway obstruction, oxidative stress and systemic inflammation.

Results: 11 in the 21 patients with CVD (52.4%) were diagnosed as COPD, 14 in 37 with DM (37.8%), and 9 in 23 with both (36.0%). Further analyses on the associations between each disease and systemic inflammation or oxidative stress were performed by logistic multivariable analyses adjusted with age, sex, smoking history, statin use, and each disease. As the results, Systemic inflammation evaluated by hsCRP was significantly higher in COPD patients. The risk of oxidative stress evaluated by 8-OHdG increased approximately 3 fold with COPD.

Conclusions: Because the smokers with DM or CVD seem to have much higher risk of COPD than smokers without them, they should be examined with pulmonary function test.

P1025
Use of a US population-based survey to describe the relationship of COPD and co-morbidities
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The Behavioral Risk Factor Surveillance System (BRFSS) is a US state-based survey that includes 90+ questions on health issues primarily related to chronic diseases. In 2007 and 2009, 6 questions were added to the North Carolina (NC) BRFSS to describe the prevalence and impact of COPD. In the 2009 NC BRFSS, there were 12,337 adults who completed the survey and 993 reported they had been diagnosed with COPD. The age-adjusted prevalence of COPD was > 5%.

The age-adjusted relative risk (RR. 95% CI) for 7 chronic diseases were compared between COPD and non-COPD: arthritis (1.64, 1.46-1.84); diabetes mellitus (1.76, 1.39-2.24); myocardial infarction (2.58, 2.0-3.33); coronary artery disease (CAD) (3.49, 2.5-4.9); stroke (2.47, 1.9-3.2); kidney disease (2.85, 1.89-4.3); current asthma (7.5, 6.24-9.3); 3 of these co-morbidities (4.95, 3.9-6.3). About 1 in 5 persons with COPD had 3 or more of these co-morbidities compared to 1 in 40 persons without COPD. One of the 6 BRFSS questions in 2009 addressed the use of prednisone in the prior year in persons with COPD. The RR of prednisone use in COPD patients with any of the co-morbidities were: arthritis 1.15 (0.89-1.48); diabetes mellitus 0.73 (0.47-1.11); myocardial infarction 1.0 (0.66-1.68); CAD 1.86 (1.02-3.38); stroke 1.28 (0.67-2.43); kidney disease 1.77 (0.77-4.07); current asthma 1.48 (1.08-2.03); 3 of these co-morbidity 1.44 (0.95-2.2). Increased prednisone use in concurrent asthma and COPD is expected whereas increased likelihood of receiving prednisone in patients with concurrent COPD and CAD is an unexpected finding, possibly related to severity of disease in these patients.

P1026
Prevalence of anemia of chronic disease in patients with chronic obstructive pulmonary disease
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Background: Anemia of chronic disease (ACD) is a disorder occurring in subjects with chronic immune activation. Chronic Obstructive Pulmonary Disease is characterized by systemic inflammation, so it could be accompanied by ACD.

We recruited for this study. All the participants were examined for pulmonary function test with bronchodilator, urine 8-OHdG/Creatinine, plasma levels for TNF-α, hs-CRP and pentoxifylline as predictors of airway obstruction, oxidative stress and systemic inflammation.

Results: 11 in the 21 patients with CVD (52.4%) were diagnosed as COPD, 14 in 37 with DM (37.8%), and 9 in 23 with both (36.0%). Further analyses on the associations between each disease and systemic inflammation or oxidative stress were performed by logistic multivariable analyses adjusted with age, sex, smoking history, statin use, and each disease. As the results, Systemic inflammation evaluated by hsCRP was significantly higher in COPD patients. The risk of oxidative stress evaluated by 8-OHdG increased approximately 3 fold with COPD.

Conclusions: Because the smokers with DM or CVD seem to have much higher risk of COPD than smokers without them, they should be examined with pulmonary function test.

P1027
The association between asthma, atopic diseases and metabolic factors in a young population of southern Taiwan
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Background: Previous studies have suggested that obesity and cholesterol may play a role in the susceptibility for asthma. The relationship between cholesterol concentrations, asthma and atopic diseases is still controversial.

Objective: The aim of this study was to investigate whether metabolic factors are associated with asthma and atopic disease.

Methods: The cross-sectional study sampled randomly 6838 subjects ≤ 18 years old from elementary, junior and senior high schools in southern Taiwan. All subjects completed questionnaire interview, weight and height data measurements and blood sample collection. Allergic disorders were determined by the subjects ever been diagnosed by a doctor. Body mass index (BMI), blood pressures, the levels of triglyceride and total cholesterol were measured.

Results: We found a significant association between high concentrations of cholesterol and dermatitis in girls (aOR = 1.56, p = 0.002) and rhinitis in boys (aOR = 1.31, p = 0.038) after adjusting for potential confounding factors. Obesity was statistically significant associated with dermatitis (p = 0.008) and rhinitis (p = 0.038). The interaction effect of cholesterol and obesity on dermatitis was significant (p = 0.032). We did not find that cholesterol and triglyceride concentrations were associated with asthma.

Conclusion: We found that high concentrations of cholesterol were associated with dermatitis in girls and rhinitis in boys. Obesity and high concentrations of cholesterol may increase the risk of dermatitis.

P1028
Epidemiology of allergic rhinitis in asthmatic patients in Greece
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Background: The co-morbidity of allergic rhinitis and asthma is a fundamental issue of common airway disease.

Objective: This study was designed in order to evaluate the co-existence of allergic rhinitis in asthmatic patients in Greece.

Methods: Data from 2700 patients with diagnosed asthma and nasal symptoms were recorded during a scheduled or an urgent visit to a specialized physician. The review was performed by respiratory physicians and allergologists. Recordings were based to a common study questionnaire.

Study population: A total of 2588 asthma patients were finally evaluated. The age range was 43.7 years with a small prevalence of female gender. One third of asthmatic patients were smokers.

Results: 62% of asthmatic patients were atopic and 53% of them had a positive asthma family history. 80.7% of asthmatic patients also had symptoms from allergic rhinitis. Nasal symptoms showed significant seasonal distribution with major peaks in spring (70%) and autumn (32%). In 60% of the cases the allergic rhinitis symptoms affect daily activities and in 72% they deteriorate asthma symptoms. Despite the use of appropriate treatment, asthma was not well controlled in 49% of the cases. 60% of the patients had at least one asthma exacerbation in the previous year and among them 85% had 1-3 exacerbations. In addition in well controlled asthmatics who were the 40.3% of total population, 77% of the patients had used medical therapy for managing allergic rhinitis.

Conclusion: The co-morbidity of allergic rhinitis in asthmatic Greek patients is high and needs to be always addressed and managed properly in order to achieve a better asthma control.

P1029
Asthma and obesity: Epidemiological data in young adults
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In recent years, several studies have found an increase in the prevalence of asthma among obese patients, but the exact nature of this association has not been fully elucidated. The aim of this study was to assess the association between asthma and obesity in 23- to 25-year-old Brazilian adults.
This was a cross-sectional analysis of 1922 men and women. Subjects completed a translated questionnaire from the European Community Respiratory Health Survey and underwent spirometry and a bronchial challenge test. Weight, height and waist circumference were measured. Multiple logistic regression analysis was carried out to assess the association of variables related to obesity and asthma, defined by the presence of symptoms and bronchial hyperresponsiveness (BHR). A self-report of a previous physician diagnosis of asthma was separately analyzed as also were socioeconomic characteristics, schooling, physical activity, smoking status, anthropometry and spirometry.

No association was detected between asthma confirmed by BHR and obesity indicators: odds ratio (OR) = 1.076 (95% CI: 0.689 - 1.680) for obesity assessed by body mass index $\geq 30$ kg/m$^2$; OR = 0.947 (95% CI: 0.686-1.308) by abnormal waist circumference and OR = 1.019 (95% CI: 0.740-1.404) by waist-to-height ratio $\geq 0.5$. A previous diagnosis of asthma confirmed by BHR and obesity, but obesity was associated with self-report of a previous physician diagnosis of asthma.

Results: The pooled effect size for coal smoke as a lung carcinogen (OR=1.82, 95% CI 1.60 to 2.06) was greater than that from biomass smoke (OR=1.50, 95% CI 1.17 to 1.94). The risk of lung cancer for combined fuel was greater in women (OR=1.81, 95% CI 1.54 to 2.12) compared to men (OR=1.16, 95% CI 0.79 to 1.69). The pooled effect size were 2.33 (95% CI 1.72, 3.17) for adenocarcinoma, 3.58 (1.58, 8.12) for squamous cell carcinoma, and 1.57 (1.38, 1.80) for tumours of unspecified cell type.

Conclusion: These findings suggest that burning of both coal and biomass is consistently associated with an increased risk of lung cancer. The review defined inadequate detection of smoking in many studies (excluded from this review) and makes recommendations for factors which must be included in future studies in this area.

P1032 Impact of air pollution control measures and weather conditions on asthma during the 2008 summer olympic games in Beijing

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The alternative transportation strategy implemented during the 2008 Summer Olympic Games in Beijing provided an opportunity to study the impact of the control measures and weather conditions on air quality and asthma morbidity.

Methods: An ecological study compared the 41 days of the Olympic Games (8 August–17 September 2008) to a baseline period (1–30 June). Also, in order to understand the impact of weather conditions on air quality, a pollution linking meteorological index (Plam) was introduced to represent the air pollution meteorological condition.

Results: Our study showed that the average number of outpatient visits for asthma was 12.5 per day at baseline and 7.3 per day during the Olympics—a 41.6% overall decrease. Compared with the baseline, the Games were associated with a significant reduction in asthma visits (RR 0.58, 95% CI: 0.52-0.65). At 16 days visit per day, asthma visits were also significantly higher, during the pre-Olympic period (RR 1.32, 95% CI: 1.15-1.52). The study also showed that the RR of asthma events on a given day, as well as the average daily peak ozone concentration during the preceding 48–72 h, increased at cumulative ozone concentrations of 70 to 100 ppb and 100 ppb or more compared with ozone concentrations of less than 70 ppb (P<0.05).

Conclusions: We concluded that along with “good” weather conditions, efforts to reduce motor vehicle traffic in Beijing during the Olympic Games were associated with a Prolonged decrease in air pollution and significantly lower rates of adult asthma events. These data provide support for efforts to reduce air pollution and improve health via reductions in motor vehicle traffic.

P1033 Indoor PM2.5 levels in homes using different types of cooking fuels in a rural Indian population and it’s association with COPD

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50% of world’s population uses biomass fuel (BMF) for cooking and heating purposes, an important risk factor for COPD.

Aim: To measure indoor particulate matter diameter $<2.5 \mu m$ (PM2.5) levels in homes that use different types of cooking fuels in a rural population, and to study its association with COPD.

Methodology: 287 homes using different types of cooking fuels (Liquefied Petroleum Gas (LPG): 91, BMF: 101, LPG+BMF: MIX: 95) were randomly selected from 22 villages. All male and female individuals above the age of 55 years residing in these homes were invited to participate. After obtaining written consent, indoor PM2.5 levels were measured using “AirMetrix” low volume sampler over 24hrs and expressed as $\mu g m^{-3}$. All subjects performed pre and post bronchodilator spirometry. COPD was defined as post-bronchodilator FEV1/FVC <70%, and small airways obstruction (SAO) as FEV2<75% $<65$s predicted.

Results: 429 subjects (mean age 45±15 years; M: 217 and F: 212) consented to participate and 266 performed acceptable spirometry. Prevalences of COPD (OR SAO were 4.9% and 24.4%, and 100% and 92% respectively, were never smokers. 24hr mean levels of PM2.5 were significantly higher in homes that used BMF verses LPG (median (IQR): BMF 236.5 $\mu g m^{-3}$ (145-414) versus LPG 109.7 $\mu g m^{-3}$ (85-172); p = 0.0001). Use of BMF was strongly associated with SAO (OR: 2.39 p<0.02) and was also associated with COPD (OR: 3.28), although this did not reach statistical significance (CI 0.8-14.23).

Conclusion: In Indian village homes, individuals in homes that use BMF have significantly higher indoor PM2.5 levels and this is strongly associated with increased prevalence of COPD and small airways obstruction.
P1034
Effects of air pollution from biomass burning in nasal mucociliary clearance of Brazilian sugarcane cutters
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Nasal mucociliary (NM) system is the first line of defense of the upper airways and it is responsible for the clearance of inhaled particles, including particulate matter (PM) from biomass burning. Several epidemiological studies have demonstrated a consistent association between levels of air pollution from biomass burning and increase in hospitalization for respiratory diseases and mortality. About 44.3% of the sugarcane is burned to facilitate the manual harvesting every year and the most exposed people are the sugarcane cutters. Nevertheless no previous reports studied respiratory effects of PM from biomass burning in these individuals. This study evaluated the effects of exposure to PM from biomass burning on NM transport after harvest. Twenty-five non-smokers (mean age = 25.7±4.5 years; BMI 23.9±2.6 kg/m²) workers in a Sugar and Ethanol Company located in Maringópolis, state of Sao Paulo, Brazil, in April 2010, were evaluated in two periods: pre-harvest season and three months after harvest. Mucociliary clearance by saccharin transit time test (STT) and nasal symptoms were assessed. STT was 7.9±3.4 min at pre-harvest and decreased significantly after harvest 3.9±2.2 min, p<0.001).

Nasal symptoms did not change following exposure. Our results suggest that acute exposure to particulate matter from sugarcane burned affects mucociliary clearance in non-smokers workers in the absence of symptoms.

P1035
The investigation of the relationship between respiratory exposures and the occurrence of the disease in patients with COPD
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We aimed to investigate the relationship with COPD and respiratory exposures. 711 patients admitted to our hospital with a diagnosis of COPD between May 2009-June 2010 were included. For the control group, 246 volunteer patients admitted to in-patient and out-patient clinics with any diagnosis other than COPD were included. Questionnaire including the questions according to socio-demographic characteristics, environmental and occupational exposures, patterns of tobacco use and passive-tobacco-smoke exposure of the patients was filled with face-to-face interview method.

The mean age was 62.7±10.8 for COPD and 64.9±10.9 for the control group (p=0.05). The average monthly-income-levels and educational-status of the patients for COPD group was significantly lower than the control group (p=0.015, p=0.002, respectively). In COPD group the number of people dealing with farming were greater than the people in the control group (p=<0.001) Tandoor and fireplace were more commonly used by women with COPD (p=0.034 and p=0.002, respectively). Smoking rates in both groups were similar. However, duration of smoking and the amount of cigarette-consumption in COPD group was higher than the people in the control group (p=0.018, p=0.001, respectively). In childhood-period, exposure to passive smoke and life-long-exposure-time in COPD group were statistically higher than the people in the control group (p=0.015, p=0.001, respectively).

For the development of COPD, except smoking, biomass-fuels and environmental exposures including passive exposure to tobacco smoke, environmental and occupational exposure to pollutants are also important risk factors, and prevention of exposure to these pollutants impede the development of COPD significantly.

P1036
Prenatal environmental tobacco smoke exposure and children's respiratory health
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Background: Exposure to environmental tobacco smoke (ETS) is associated with respiratory symptoms. Prenatal ETS exposure is associated with impaired lung function and wheezing illnesses, particularly in preschool children. Although negative impact of prenatal ETS exposure on children is evident, ETS impact on respiratory system of infants is still poorly explored.

Purpose: To assess the possible effects of ETS exposure in utero on lower respiratory disease in children from infants up to seven years of age.

Methods: We evaluated the health impact of ETS in 117 infants born from asthmatic mothers. We also analyzed the onset of wheeze & asthma by the age of 7 with regard to the impact of ETS.

Results: The prevalence of wheeze during the first year of life was 4.7 times higher in infants who were prenatally exposed to ETS (OR-4.69 [CI:1.63-13.52]) compared to children without ETS exposure. However, no differences in allergic asthma prevalence by 7 years of age were found between the patient groups.

Conclusions: The research results provide strong evidence linking prenatal ETS to impairments in infants’ respiratory system.

P1037
Inhaled black carbon in the lower airways of London cyclists
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Background: Inhalable elemental black carbon (BC) from fossil fuel combustion impacts lung health. We recently developed a novel method for assessing internal dose of BC using the ambient black carbon (BC) mass (BCm) obtained from a project (BCm). To date, the determinants of BCm in healthy individuals living in urban areas remain unclear. Personal external monitoring indirectly suggests that cyclists have high levels of BC exposure.

Aim: To compare BCm in healthy adult cycling (cyclist) and non-cycling (pedestrian) London commuters.

Methods: AM carbon was assessed in non-smoking urban commuters aged 18 to 40 yr. AM were sampled using a passive BC filter, e.g., Teflon filter (STT) and nasal symptoms were assessed. STT was 7.9±3.4 min at pre-harvest and decreased significantly after harvest 3.9±2.2 min, p<0.001).

Cyclists had significantly more AM carbon than pedestrians (Chart 1).
air pollutants exposure and lung obstruction was explored by logistic regression analysis.

**Results:** In both studies T-R air pollutants concentrations were statistically significant higher (p<0.05) in the vicinity of road in comparison to rural areas. The significant association between living close to a busy road and risk of obstruction was found. In the Warsaw study risk was 4.35 times higher (95% CI: 2.57-7.35) among non-smoking inhabitants of the city compared with rural area residents. The second study resulted in similar observations – the risk was 3.16 times higher (95%CI: 1.09-9.16). Amid smokers the difference in risk of obstruction between urban and rural areas was insignificant.

**Conclusion:** Presumably high T-R air pollutants concentration in the proximity of main roads is one of the significant reason of airways flow limitation. Therefore the risk of obstruction highly depends on place of living, particularly among non-smoking people.

**References:**

P1039

**Effect of daily pollution exposure in the autonomic system in traffic workers of Sao Paulo**

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**Background:** Heart rate variability is used to quantify autonomic response and to detect cardiovascular diseases. Chronic pollution exposure is known to increase arterial pressure and the incidence of cardiac ischemia leading to cardiovascular diseases and death; however, the effect of variation of daily pollution in chronically exposed subjects remains poorly known.

**Objective:** To study the effect of acute pollution exposure in the autonomic system at rest and exercise in traffic workers.

**Methods:** Twenty-one male subjects were studied in 4 randomized working days (once a week) with distinct pollution exposure. The amount of pollution (ozone (O3) and nitrogen dioxide (NO2)) was measured 24 hours before the day test by a pollution analyzer. Activity of autonomic system response was measured during 8 minutes either at rest or during treadmill exercise (moderate intensity).

**Results:** The levels of pollution exposure were considered intermediate and ranged from 123.9 μg/m3 to 317.2 μg/m3 and 0.1 μg/m3 and 26.3 μg/m3 respectively (of NO2 and O3). In the days with higher levels of pollution, it was observed a reduction in the activity parasympathetic system (RMSSD) at rest (p<0.05). In addition, it was observed a linear correlation between the levels of pollution and a reduction in the RMSSD measure at rest (p=0.52; p=0.01). Interesting, during exercise, the parasympathetic response was increased in the most polluted days (p<0.05).

**Conclusion:** Our results suggest that even low changes in daily pollution exposure selectively modify the autonomic system to either rest of exercise. Supported by CNPq.

**References:**

P1040

**Non-malignant abnormalities by chest radiography and high-resolution computed tomography in millers and miners with different levels of asbestos exposure**

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The diagnostic performance of high-resolution computed tomography (HRCT) and conventional chest radiography (CXR) has not been compared on a large sample of subjects with widely-different degrees of cumulative exposure to asbestos, i.e., with ample differences in pre-test likelihood of disease. We evaluated 1427 ex-workers in chrysotile mills and mines who were separated into 4 groups (Gr) of decreasing cumulative exposure (Groups I to IV). The prevalence of either parenchymal or pleural abnormalities were markedly reduced as exposure decreased (p<0.01). Assuming HRCT as the criterion standard, CXR was associated with increased false-positive and false-negative rates for parenchymal and pleural abnormalities, respectively. These findings were consistent across the groups of asbestos exposure (table).

<table>
<thead>
<tr>
<th>Exposure Period</th>
<th>Parenchymal</th>
<th>Pleural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr I (1940–1966)</td>
<td>17 (13.7)</td>
<td>14 (11.3)</td>
</tr>
<tr>
<td>Gr II (1967–1976)</td>
<td>44 (7.3)</td>
<td>26 (4.3)</td>
</tr>
<tr>
<td>Gr III (1977–1980)</td>
<td>23 (4.8)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Gr IV (after 1980)</td>
<td>5 (2.3)</td>
<td>3 (1.4)</td>
</tr>
</tbody>
</table>

**References:**

P1041

**Acute respiratory effects in atopic humans exposed to short-term controlled exposure to diluted wood smoke**

Ingunn S. Riddervold1, Jakob H. Bønløkke1, Anna-Carin Olin2, Vivi Schlünssen1, Torben Sigsgaard1, *1Department of Occupational and Environmental Medicine, School of Public Health, Aarhus University, Aarhus, Denmark; 2Division of Occupational and Environmental Medicine, Sahlgrenska University Hospital and Academy, Öthenburg, Sweden*

Growing evidence suggests that particulate air pollution derived from wood stoves causes acute inflammation in the respiratory system and possibly increases the incidence of asthma and other respiratory diseases. The aim of this study was to evaluate acute respiratory effects from short-term wood smoke exposure in humans. A total of 20 non-smoking atopic subjects with normal lung function and without bronchial responsiveness completed the study. The subjects were monitored during three different experimental exposure sessions, aiming at particle concentrations of 200μg/ml, 400μg/ml, and clean air as control exposure. A balanced cross-over design was applied and the subjects were randomly allocated to exposure orders.

Diluted wood smoke were generated in a wood-burning facility and added to a full-scale climate chamber exposure lasted for 3 hours under controlled environmental conditions. Respiratory effects were evaluated at baseline and follow-up measurements during exposure in relation to changes in lung function and were assessed in relation to changes in airway inflammation status measures by fractional exhaled nitric oxide (FENO), exhaled breath condensate (EBC) and nasal lavage (NAL, samples). No statistically significant differences between the three exposures were found for any of the lung function outcomes. FEV1 (p=0.6283); and FVC (p=0.8364), or for FeNO (p=0.3578). Mild signs of airway inflammation were found in few of the analyzed markers of inflammation in the NAL and EBC samples. In conclusion, short term exposure with wood smoke causes only mild inflammatory response.

**References:**

P1042

**Biodiesel usage in Austria: Improving or deteriorating respiratory health?**

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We estimated respiratory health outcomes for two scenarios for the fraction of biodiesel used in road vehicles: B10 a blend of 10% bio- and standard diesel; B100 biodiesel only.

Data of the composition of vehicle exhausts, vehicle frequency and exhaust volumes were entered into a dispersion model to obtain estimates for the change in particulate matter (PM10, PM2.5) and nitrogen dioxide (NO2) for Vienna and the surrounding region (Lower Austria). From established exposure-response relationships the health impacts (respiratory mortality and hospital admissions) of the scenarios were expressed as a difference to the reference scenario (year 2007). Impacts of B10 were very small. For B100 fine particles would decrease by 4% (countrywide) to 8% (city of Vienna) while NO2 would increase by 11% in Vienna. Based on effect estimates for chronic exposure the reduction of PM2.5 would lead to 53 less cardiopulmonary annual deaths. Effect estimates based on time series studies resulted in smaller numbers: Reduction of ambient PM10 levels were estimated to result in 8 less annual respiratory hospital admissions. Concerning respiratory mortality the increase of NO2 could result in additional 20 premature deaths per year, while the beneficial effect of the reduction in particles only would lead to a reduction of one case per year.

If health impacts of these air pollutants were independent, the increase in NO2 would strongly outweigh the reduction of PM2.5. However, dose-response relationships of PM and NO2 are not independent and NO2 is indicating traffic related exposures as is PM2.5. Therefore the adverse impact might be less pronounced than indicated by the net difference.

**References:**

P1043

**Relation between fractional exhaled NO and lung function and exposure to ambient particulate matter from contrasting sources**

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Epidemiological studies demonstrated the adverse health effects of ambient particulate...
late matter (PM) but it is not clear which specific characteristics (size, components) or sources of PM are responsible for the observed effects. The aim of the RAPTES project is to establish which specific characteristics of ambient PM are responsible for health effects associated with PM. To address this we combined exposure of volunteers with real-world exposure conditions at sites with high contrast and low correlation between PM characteristics.

30 young, healthy volunteers were exposed multiple times at different sites in the Netherlands: two traffic sites, underground train station, farm and an urban background site. Exposure of volunteers and air pollution characterization took place on 30 consecutive occasions. Particle number concentration (PNP, ultrafine particles) and total oxidative potential were not associated with changes in FENO or lung function parameters. An increase in FENO and decrease in lung function were observed in young, healthy volunteers after five-hour exposure to ambient air pollution, specifically associated with high concentrations of ultrafine particles and not with other major PM characteristics.

P1044 Short-term effect of ozone in a panel study of asthmatics
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Introduction: Particulate matter, exhaust and ozone concentrations in ambient air have been associated with respiratory effects, and asthma is especially sensitive.

Aims: Our objective was to study short-term effects of particles (PM10), vehicle exhaust (NO2) and ozone in relation to lung function among adults with asthma residing in the two major Swedish cities Stockholm and Gothenburg.

Methods: 797 adults (17 females) with asthma recorded from the GAZLEN survey (aged 25-72 years) used a daily diary over a 10 week period (winter-spring) and recorded peak expiratory flow (PEF), forced expiratory volume in the first second (FEV1). We collected urban background concentrations of PM10, NO2 and ozone in the city centre, and adjusted for participant (intercept), time trend, day of week, temperature and humidity in the regression analysis. We evaluated the effect of the same day concentrations, and lagged one and two days, respectively.

Results: 37% of ozone lag 0, lag 1, lag 2 and lag 0-2 were seen in both cities, some significant. In Stockholm there was also a significant negative effect of ozone on PEF. No significant effects were seen for PM10 or NO2.

Discussion: We found the most consistent negative effects on lung function of ozone. Fluctuations in daily mean concentrations of PM10 and NO2 may be less well represented by a central monitoring station.

P1045 The effects of whole life arsenic exposure via drinking water on airway hyperresponsiveness in C57BL/6 mice
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Background: Arsenic exposure via drinking water is a significant global environmental health issue. Epidemiological data suggest a relationship between arsenic exposure and the development of obstructive lung disease.

Aims: We aimed to determine if whole life arsenic exposure via drinking water impacts lung function and results in airway hyperresponsiveness.

Methods: Pregnant C57BL/6 mice were exposed to drinking water containing 0 (control) or 100μg/L arsenic from gestational day 8 to parturition. After birth, offspring were exposed to arsenic (or control) in breastmilk/drinking water until the next morning. PNC was also associated with an about 1% decrease in FEV1 and FVC at almost all measured time points. PNC, PM2.5 and total oxidative potential were not associated with changes in FENO or lung function parameters.

Discussion: Studies have shown that mice exposed to arsenic throughout life have impaired baseline lung function and airway hyperresponsiveness as adults. These findings support the notion that ingested arsenic is a novel respiratory toxin and may be an important risk factor for the development of obstructive lung disease in arsenic exposed populations.

P1046 Carbon content of airway macromolecules and lung function in children within the London low emission zone (LEZ)
Thomas Round 1, Dev Gadgil 1, Isobel Dundas 1, Iain Dickson 1, Naseem Mushtaq 1, Helen Wood 1, Jonathan Grigg 1, Chris Griffiths 1, Centre for Health Sciences, Barts and The London School of Medicine, London, United Kingdom; 2Environmental Research Group, Kings College, London, United Kingdom

Introduction: The London Low Emission Zone (LEZ) was introduced in 2008 with the aim of reducing traffic emissions to improve respiratory health. Increased airway macromolecule carbon (AM) content is associated with decreased FEV1.

Aims: Investigate the association between AM carbon and lung function as part of a larger study into impact of the LEZ on children’s respiratory health.

Methods: Cross sectional study of children aged 8-9 within schools. Sputum induction with nebulised 4.5% saline. Nebulisation extended from 15 to 20-30 minutes. Sputum processed with standard techniques. Images were obtained for 50 random AM per child. AM carbon was assessed using imaging software. Analysis of mean carbon area per cell with lung function and distance from main road was performed.

Results: 2008-10, 20 schools and 619 children taken part in LEZ study, with 59 (9.5%) attempting sputum induction. Standard 15 minute nebulisation led to a sample yield of 20%, compared to modified nebulisation (mean 22.55 minutes) with 52% yield. 15 samples so far have identified macrophages, 13 suitable for imaging.

Discussion: Spearman rank correlation for carbon area per cell were negative for% predicted FEV1 (r=-0.32) and distance from main road (r=0.1).

Conclusion: Sputum induction is practical and acceptable within schools. Prospective data suggests that modified nebulisation can improve sample yield. Further children will be recruited over the next 2 years to investigate this potential association and applicability to future research.

P1047 Copper nanoparticles generate reactive oxygen species (ROS) after air delivery to alveolar type-II cells in vitro
Peter S. Thorne 1, Jong Sung Kim 2, Andrea Adamcakova-Dodd. Occupational and Environmental Health, University of Iowa, Iowa City, IA, United States

Rapid screening methods for NP are needed that replicate in vivo toxicity. We assessed cytotoxicity and ROS generation from Cu NP using an in vitro dynamic exposure model (IVDEM) that overcomes limitations of submerged-cell methods and mimics in vivo exposure conditions by generating and depositing airborne NP directly onto cells grown at an air-liquid interface (ALI). A549 cells were exposed to particle-free air or Cu NP aerosols (12±1 μm) for 4 h at 0.4 μg/cm² after which cells were incubated for 4, 8, 12, or 24 h. Cytotoxicity was assessed by Alamar Blue assay of mitochondrial function and ROS using carboxy-H2DCF-DA as an indicator of steady-state levels of pro-oxidants. Aerosolized Cu NPs were 30 nm (σ=1.9) indicating that the system produced a nanoscaled distribution of NP. Direct exposure of cells at the ALI mimics agglomeration and retained inherent particle characteristics. Viability for cells exposed to particle-free air or Cu NPs for 4 h were no different than cells maintained in the incubator (controls) indicating no trauma associated with exposure in the IVDEM. The production of intracellular ROS in particle-free, air-exposed cells was the same as controls. However, intracellular ROS levels after Cu NP exposure increased at 4 and 8 h post-incubation (130% and 170% of control). ROS levels resolved to baseline at 24 h postexposure indicating that Cu NP-induced oxidative stress did not exceed the cells’ ability to neutralize ROS. Cu NPs generate significant intracellular ROS after air-delivery to human alveolar cells in this IVDEM. This in vitro test system using lung epithelial cells with an ALI has potential utility for NP toxicity assessment.

SUNDAY, SEPTEMBER 25TH 2011
from 2001 to 2003 daily records: of attendances at São Paulo Hospital Emergency Unit (SPHEU) with ICD 10th J01-J06, of levels of PM2.5, NO2, SO2, CO, and O3, of temperature and humidity.
GLM Poisson regression was adopted using daily number of AURTI visits as de- pending variables. Long-term trend was controlled by a semi parametric function. Linear terms were used for temperature and humidity. Effects were presented as percentage increase and 95% CI in AURTI SPHEU visits due to interquartile range increases in air pollutants daily levels. During the study period, 177,325 visits occurred in the SPHEU and 137,530 (72%) were due to AURTI.

In terms of age groups, emergency visits of children and younger than 13 years of age were the most frequent, followed by the groups 40 to 65 years, 30 to 39 years, older than 64 years and adolescents from 13 to 19 years old. PM2.5 presented effects at lag zero on daily visits due to AURTI and this pattern was observed for all age groups. Among those younger than 13 years of age this effect started at lag zero (2.1%; 95% CI 0.9- 5.8) and remained almost four days. NO2, SO2, and O3 presented effects at lag zero. URKI cannot be considered severe health outcomes. However, it is one of the most frequent groups of respiratory diseases and affects different age groups. Despite of the well-known respiratory symptoms, there are other age groups to present susceptibility enlarging the burden of air pollutants on health.

Conclusion: Symptoms of anxiety and depression are common among people with long term exposure to indoor air pollution and they usually go undiagnosed due to low accessibility to proper health facilities. They should be routinely screened for psychiatric morbidities.

106. Mineral dusts

P1051
The frequency and factors for occurrence of asbestos-related diseases in the rural of Sivas localised on central Anatolia (cross sectional epidemiologic study)

Isa Dongel1, Mehmet Bayram2, Huseyin Yalcin4, Sefa Gul turk4, Nur Dilek Bakan5.

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Objective: To determine the rate and affecting factors of asbestos-related diseases (ARD) in the villages close to ophiolitic units in the rural of Sivas, central Anatolia in Turkey.

Methods: Volunteers (age>35, >20 years resident) from villages close to ophiolitic units and from villages >20 km distant to ophiolitic units as control group were included. Chest X-rays and questionnaire for demographical data and respiratory symptoms were performed. A geological map was used to measure the distance between ophiolitic units and villages. Samples were taken from houses and soils and analyzed for asbestos with X-ray diffraction.

Results: 2947 volunteers (1148 male, 1839 female) from 48 villages close to ophiolitic units and 157 (91 male, 66 female) volunteers from 6 villages far to ophiolitic units were included. Mean age of study and control groups were 55.2 and 57.3 respectively. 292 patients (3 malignant mesothelioma, 289 pleural plaque) with ARD were identified from villages close to ophiolitic units. No ARD was identified in control group. Factors affecting ARD risk were male sex (OR 3.1;p=0.00), advanced age (OR 1.05 for every year of age;p=0.00), residency close to ophiolitic units (for each 1 km 12% increase) and, decrease in BMI (for each 1 unit 3.6% increase) in multivariate logistic regression analysis. Serpentinite was found in samples of villages close to ophiolitic units, no asbestos was found in control villages.

Conclusion: ARD rate is high in residents close to ophiolitic units in rural Sivas. Factors associated with ARD development were advanced age, male sex and living close to ophiolitic units.

P1052
The impact of residential proximity to ophiolitic units in the development of asbestos-related diseases

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Objective: To determine the relation between risk of asbestos related diseases (ARD) and the proximity of birthplaces to ophiolitic units (OU) which contains serpentine in the province of Sivas, Turkey.

Method: Records between 2000 and 2010 of mesothelioma, pleural plaque (PP), prostate cancer and breast cancer patients from cancer registry were reviewed. Samples were obtained from indoor plasterers and source of plasters. Birthplaces of patients were marked on a map with OU modified from geological map (mesothelioma: red square, PP: black star and OU: green areas).
The distance between residential area of birthplace of the patients and OU were measured.

**Result:** Birthplaces of 100 mesothelioma, 133 PP, 161 prostate cancer and 139 breast cancer patients were included. Samples of plasters and soil were identified as 95% serpentine. Mean distance to OU of patients with ARD and control cases were 5.9 and 15.9 kilometers.

Logistic regression analysis after age adjustment between groups showed that risk for ARD increased with decrease of distance to OU (Odds ratio: 1.72 for every 5 km decrease).

**Conclusion:** The proximity of birthplace to OU increases the risk of ARD.

**P1053**

CO-diffusion capacity in asbestos-exposed workers with or without abdominal chest X-ray findings

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1Department of Clinical Occupational Medicine, Institute for Occupational and Maritime Medicine, Hamburg, Germany; 2Gesundheitmanagement Hamburg, Vattenfall Europe Business Services GmbH, Hamburg, Germany

**Background:** Exposure to asbestos can cause a restrictive lung disorder with impaired pulmonary gas exchange. It is controversial, whether lung function impairments occur in the absence of radiological abnormalities.

**Aim:** To assess CO-diffusion capacity in asbestos-exposed workers according to radiological findings.

**Methods:** Medical surveillance of 63 male workers formerly asbestos-exposed included a comprehensive medical and occupational history. All subjects underwent spirometry and body plethysmography according to ATS/ERS quality standards. CO-diffusion capacity (DLco) was measured according to Machney et al. 2005. Results are reported as% predicted. Subjects were classified according to chest X-ray findings.

**Results:** Exposure varied widely across workers (2-420 fibre-years). Asbestosis (ILO: ≥1/1, ≥pleural fibrosis) was found in 4 workers, 18 had pleural fibrosis and 41 had normal chest X-ray findings. Pulmonary gas exchange was reduced in all three groups: DLco 51% (95%-CI 24%, 78%), 73% (95%-CI 65%, 81%) and 84% (95%-CI 79%, 89%), respectively. DLco was below the lower limit of normal in 37 cases. Mean DLco of never smokers (n=12), ex smokers (n=24), and smokers (n=3), all with normal chest X-ray, was 85% (95%-CI 77%, 93%), 84% (95%-CI 76%, 91%), and 84% (95%-CI 70%, 99%), respectively. We found no statistical association between DLco and fibre-years.

**Conclusions:** We detected significantly impaired gas exchange in all three groups: DLco 51% (95%-CI 24%, 78%), 73% (95%-CI 65%, 81%) and 84% (95%-CI 79%, 89%), respectively. We found no statistical association between DLco and fibre-years.

**Background:** Relationships between isolated parietal plaques and lung function in asbestos-exposed workers free from pleural fibrosis was found in 4 workers, 18 had pleural fibrosis and 41 had normal chest X-ray findings. Pulmonary gas exchange was reduced in all three groups: DLco 51% (95%-CI 24%, 78%), 73% (95%-CI 65%, 81%) and 84% (95%-CI 79%, 89%), respectively. DLco was below the lower limit of normal in 37 cases. Mean DLco of never smokers (n=12), ex smokers (n=24), and smokers (n=3), all with normal chest X-ray, was 85% (95%-CI 77%, 93%), 84% (95%-CI 76%, 91%), and 84% (95%-CI 70%, 99%), respectively. We found no statistical association between DLco and fibre-years.

**Conclusions:** We detected significantly impaired gas exchange in all three groups: DLco 51% (95%-CI 24%, 78%), 73% (95%-CI 65%, 81%) and 84% (95%-CI 79%, 89%), respectively. We found no statistical association between DLco and fibre-years.

**Methods:** The study population consisted of 2,743 subjects included in a large-scale pilot screening program for asbestos-related diseases in four regions of France between 2003 and 2005. All had been occupationally exposed to asbestos, and were free of interstitial disease on high resolution chest computed tomography (HRCT). The asbestos exposure was assessed with calculation of an individual cumulative exposure index (CEI) taking into account all job periods for each subject. Each included subject benefited from pulmonary function tests (PFT) and HRCT was interpreted by a panel of expert radiologists in thoracic imaging. In both univariate and multivariate analysis, variables were adjusted on tobacco status, body mass index (BMI), CEI to asbestos and the center where PFT were made.

**Results:** Isolated pleural plaques were associated with a significant decrease of TLC (p=0.049), FVC (p=0.001) and FEV1 (p=0.003). On the other hand, no significant relationship was observed between pleural plaques and FEV1/FVC ratio. FEF25-75% and RV. A significant correlation was found between the extent of pleural plaques and the reduction of FVC (p trend=0.0089) and TLC (p trend=0.0464). By contrast, thickness of pleural plaques was not related to any functional impairment.

**Conclusions:** Our results are in favor of a relationship between isolated parietal and/or diphragmatic pleural plaques and a trend to restrictive pattern.

**P1055**

Respiratory morbidity of children exposed to crocidolite at Wittenoom, Western Australia

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Little is known about the general respiratory health of people exposed to asbestos in childhood. This study investigated respiratory symptoms and lung function in subjects who lived in an asbestos mining town (Wittenoom) as children. Lung function (spirometry), chest x-ray, and respiratory symptom data from former Wittenoom children who participated in an Asbestos Review Program (ARP) were assessed. Symptom frequencies and predicted FVC, FEV1 and FEV1/FVC were calculated. Predicators of increased symptoms and poor lung function were assessed using linear and logistic regression. 186 individuals of the ARP had been children when living in Wittenoom. Of these, 8 had developed mesothelioma, 2 lung cancer, 14 radiographic asbestos and 3 diffuse pleural thickening. These participants were excluded from the analyses. The median age of arrival was 2.3 (95% CI 0.6 – 6.0) years and the median duration of residence was 24 (12 - 48) months. The mean age at assessment was 48.5 (SD 9.3) years. About 25% were past smokers and 22.7% still smoked at the time of the assessment. Reported symptoms included: cough (15.7%), phlegm (11.6%), dyspnea (18.3%), wheeze (20.1%) and asthma (20.8%). The main predictor for increased symptoms was current smoking. Mean (SD) predicted FVC, FEV1 and FEV1/FVC were 90.6% (21.4), 90.1% (20.4) and 79.5% (21.1), respectively. Age at time of test, age at 1st exposure and cumulative asbestos exposure were associated with both reduced FVC and FEV1. Age at time of test, being male and asthma were associated with decreased FEV1/FVC. Asbestos exposure as a child is associated with sub-clinical restrictive lung function decrements even in the absence of radiographic abnormalities.

**P1056**

The sociodemographic and clinical characteristics of Turkish workers with pneumoconiosis

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Pneumoconois is an irreversible, preventable disease caused by dust inhalation. Although in other countries, by precautions the incidence decreased to 0.3–5%, it is still 10-15% in our country in pneumoconiosis causing occupations. We aimed to describe the characteristics of our 208 pneumoconiosis workers admitted to Istanbul Occupational Disease Hospital. Patient files between 01st Jan 2008 and 31st Dec 2010 are used for the descriptive study. All of the patients were male with 38,82±13 years of age. The most common workplace was Gaziosmanpasa with 27 cases. The mostly seen works were denim sandblasting, dental technicians, coal mining and casting (%50,5,%12,%6,7,%4,8). The most exposure material was silicium (86,5%). Mean exposure time was 9,9±8,9 years. Profusion according to the ILO classification was in the table. In 37 cases, there was an A opacity and B opacity in 28. The mean FEVI% was 67,27±23.3, FVC% 77,8±20,86, FEV1/FVC%85,1±16 and KeC 102,74±28,1. The period between exposure and

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Radiographic profusion
symptoms were calculated at 10.48±8.7 years. Patients were mostly referred by a social security center, secondly by Sureyyapasa training hospital and thirdly, admitted by themselves. The most common symptoms were breathlessness, cough and exertional dyspnea. The exposure time in a workplace is very important but in our files there were no data showing this, so we planned to rearrange our patient files. Generally each paper in the literature discusses only one type of occupation causing pneumoconiosis. To our knowledge this is the first study concerning nearly all occupations causing the disease.

P1057
Respiratory symptoms, lung function impairment, and sensitization to metals in construction workers exposed to ashes, cement and ash-cement mixtures
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Objective: To evaluate the prevalence of respiratory symptoms, lung function impairment, and sensitization to metals in construction workers exposed to ashes, cement and ash-cement mixtures.

Methods: We performed a cross-sectional study including 45 construction workers exposed to ashes, cement and ash-cement mixtures (mean age 43.1±6.8 yrs, mean job duration 19.5±7.1 yrs). In addition, 50 office workers (mean age 42.2±10.5 yrs, mean job duration 17.8±9.2 yrs) were examined as a control. Evaluation of examined subjects included completion of questionnaire on respiratory symptoms, lung function testing, histamine challenge test (PC20 ≤ 8 mg/ml), and patch testing.

Results: Compared with office workers, construction workers had more frequently respiratory symptoms (cough, phlegm, wheezing, and shortness of breath) in the last 12 months (40.0% vs. 16.0%, P<0.05). The difference was significant for cough (42.2% vs. 16.0%, P<0.05), wheezing (37.8% vs. 14.0%, P<0.05), and shortness of breath (44.4% vs. 14.0%, P<0.05). Lung function testing showed that construction workers had significantly lower FEV1 and significantly lower FVC/FVC. Significant association was registered between respiratory symptoms and BHR in both construction and office workers. Patch testing to chromium, cobalt and nickel was positive in 22.2%, 15.6%, and 8.9% of all construction workers, respectively.

Conclusion: Our data emphasize important role of specific occupational hazards in the development of respiratory symptoms, lung function impairment, and sensitization to metals in construction workers exposed to ashes, cement and ash-cement mixtures.

P1058
Cement dust exposure, respiratory symptoms and exhaled nitric oxide: A cross-sectional study
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Aim: To explore whether cement dust exposure is associated with increase in chronic respiratory symptoms and FeNO concentration among cement factory workers in Tanzania.

Methods: The exposed group comprised 171 cement production workers while 98 workers from a beverage factory served as controls. Personal total dust samples were collected from the breathing zone of workers in the cement factory (n=130) and the beverage factory (n=16). The information on chronic respiratory symptoms was collected by a questionnaire, and FeNO concentrations were measured by a NOx Mino monitor among 117 exposed and 24 controls.

Results: Geometric means of total dust exposure among control and exposed workers were 0.6 mg/m³ and 5.0 mg/m³, respectively (p<0.001). The exposed workers and controls had similar age and smoking habits. The prevalence of from being the major risk factor for lung cancer, may be a co-factor in the development of asbestos in lung disease. The Health and Safety Executive report mentions the high rate of smokers in asbestos related industry [1]. We reviewed our local population of asbestos workers to explore that.

Methods: Between 1994 and 2007, 268 workers were seen for clinical assessment, spirometry, health safety advice and smoking cessation. A retrospective analysis of records, spirometry, smoking habits, effect of smoking cessation advice, was undertaken.

Results: 268 subjects were seen, 65 on multiple occasions, 214 (79%) were involved with asbestos handling or removal. 42 (16%) worked in supervisory or managerial capacities. 12.5% were laboratory analysts. Current smoking rates for handlers was 67% (144/214), managerial group 36%, and analysts 33% (p=0.015). Ex smoking rates were 11% for removers, 38% for the supervisory and managerial group and 8% for analysts. Non-smoking rates were 22% for handlers and removers, 46% for supervisors and managers and 58% for analysts. The rate of decline in FEV1 for current smoking handlers/asbestos remover was 52.8 ml per year, and for supervisors 22.3 ml per year (p=0.0023). The mean FEV1 decline in non-smokers and ex-smokers was 37.5 ml/yr.

Conclusions: Workers with highest asbestos exposure are significantly more likely to be current smokers and to have greater decline in FEV1, conferring greater disease risk [2]. Smoking behaviour has not changed since 1983. Consultant advice on cessation was ineffective for the group most at risk.

References:
chronic respiratory symptoms was higher among exposed compared to controls; Wheezing (18% vs. 15.3%) Work related shortness of breath (15.8% vs. 6.1%), dyspnoea (13.5% vs. 9.2%), chronic spontaneous production (8.4 vs. 1.1%) and chronic cough (6.6% vs. 1.9%).

Exposed workers had higher mean FPaO2 concentrations (26.0 ppm) than controls (20.0 ppm), but the difference was not significant.

Conclusions: The prevalence of chronic respiratory symptoms and FPaO2 concentrations among exposed workers indicate an association between cement dust and airway inflammation.

P1065 Pulmonary asbestos fiber in an urban population in Spain
Maria-Isabel Velasco-García1, María-Jesús Cruz2, Carmen Diego3, Mª Angeles Montero1, Ferran Morell2, Jaume Ferrer2

Introduction: In this study, asbestos fibers in lung are characterized and quantified for the first time in an exposed and an unexposed Spanish population.

Material and methods: We studied samples from 47 autopsy specimens (25 unexposed subjects from Barcelona with no lung disease, and 22 asbestos-exposed subjects from El Ferrol), and 32 resected surgical specimens from lung cancer patients in Barcelona.

After eliminating organic material, the inorganic residue was analyzed by optic microscopy and electron microscopy. Results are expressed as the number of asbestos fibers or asbestos bodies per gram of dry lung tissue. To identify the type of fibers found, 38 samples were analyzed by scanning electron microscopy and energy dispersive x-ray analysis.

Conclusions: This study provides the first available data on the type of asbestos content in lung in the Spanish population. The exclusive retention of amphiboles was worthy of note and suggests elimination of chrysotiles following inhalation. Optic and electron microscopy were both reliable methods for pulmonary asbestos determination in our laboratory.

P1066 Serum cytokine spectrum in workers with occupational salt dust exposure in underground conditions
Nicodaj Denisiević1, Tatyana Rybina2, Elena Amelchenko2

Introduction: Cytokines are circulating cellular mediators of the immune response, hematopoiesis, inflammation and development. The aim of this study was to assess the level of cytokines in workers with occupational salt dust exposure in underground conditions.

Methods: We studied 49 workers with occupational salt dust exposure with mean age 39.7 ± 7.0 years, length of work in underground conditions 9.7 ± 5.5 years. The control group included 17 healthy men 46.9 ± 8.3 years without occupational hazards. Serum levels of IL-8, IL-2, TNF-α, INF-γ were measured by ELISA.

Results: The concentration of all studied cytokines in serum of workers with occupational salt dust exposure engaged in underground working conditions was lower vs the control group. We revealed a significant decrease in INF-γ values (p = 0.0226) (4.30 [0.30, 12.8] pg/ml vs 11.8 [3.80, 19.8] pg/ml). In our opinion, decreased cytokine values in workers engaged in underground working conditions could possibly relate from the reduced activation of T-lymphocytes and NK-cells.

Conclusions: Low bacterial and viral antigens exposure of underground workers, daily respiratory tract clearance during the work shift (bacteriostatic and bactericidal effect on microorganisms of the salt dust) probably contributes to the reduction of cytokine production.
P1067
Occupational and environmental determinants of exposure to asbestos in malignant mesothelioma cases
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Background: The relationship between pleural malignant mesothelioma and exposure to asbestos is currently known, but there is no accurate information regarding high-risk occupations and types of exposure in Iran.

Aim and objectives: As Asbestos is still used in Iran intake of ban in many other countries, in this study we specified high risk jobs for asbestos exposure and further intervention.

Methods: In this case-control study, 64 cases with diagnosis of pleural malignant mesothelioma who were admitted in Masih daneshvari hospital between 2001 and 2009 were studied. All the cases and 55 controls participated in a telephone interview for job history and occupational and environmental exposures to asbestos.

Results: Asbestos exposed occupations in mesothelioma group included corrugated asbestos cement sheet production 11 (%17.2), Insulation 6 (%9.4), and car brake shoe manufacturing 2 (%3.1). In control group the only exposed occupation was construction 8 (%13.79). Odds Ratio calculated for occupational exposure to asbestos was 5.51 (CI=2.26-13.47). Residency in neighbourhood of corrugated asbestos cement sheet production factory was the most prevalent cause for environmental exposure.

Conclusion: In 46.87% of mesothelioma cases, source of exposure to asbestos was corrugated asbestos cement sheet industry due to employment in the factory, residency in neighbourhood of the factory or use of its products.

P1068
Investigating of CEA, CA125, CA15-3, CA19-9, TF3, TF4, TSH, vitamin B12, folic acid and ferritin in malignant and benign diseases due to environmental asbestos exposure
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Aim: To identify several biochemical marker levels in mesothelioma (MM), in subjects with pleural plaques (PP) due to environmental asbestos exposure (EAE) and in healthy subjects with EAE.

Method: 277 patients with PP from villages close to asbestos-containing units (OU) (serpentinite asbestos containing). 121 healthy subjects from villages close to OU, 118 healthy subjects without EAE and 24 MM patients were included to the study.

Table 1: Distribution of sex, age and biochemical findings according to the groups

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107. Smoking cessation science and smoking-related disorders

P1070
Smoking cessation – What determines adherence to pharmacological treatment
Ana Castro, Júlia Valério, Albertina Correia, Miguel Guimarães, Ivone Pascoal.
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Introduction: Cigarette smoking is the 1st modifiable risk factor for premature morbidity and mortality. Treating smokers is the best cost-effectiveness health care intervention.

Objective: Assess adherence to pharmacological treatment and factors influencing it. Correlate variables determining adherence and results at the end of treatment and 12 months follow up.

Methods: Characterization of a patients sample whom was prescribed Varenicline or Nicotine Replacement Therapy (NRT). Analyse and correlate treatment adherence with factors affecting adherence (motivation, dependency, household smoking habits, side-effects,etc).

Results: 166 smokers were included, 71% male, 28% female, mean age 49 years. Mean tabagic burden: 45pack-years. Mean motivation 8.1–Richmond test (RT); mean dependence 5.1–Fagerström test (FT). Varenicline was proposed to 48% and NRT to 51%. 55% of patients followed the treatment correctly and the others discontinued therapy. Reasons given for non-compliance: unrecognized therapeutic effect, excessive self-confidence, price, side effects. The patients that completed treatment, 52% did not smoke at the end of treatment and 55% were nonsmokers at the end of 12 months follow up. There was a positive correlation (Spearman correlation)
Correlation,p<0.05) of adherence with: RT, educational level and NRT therapy. Negative correlation with: household smoking habits, FT.

Conclusion: Treatment adherence is a key factor for smoking abstinence. In our group, adherence was higher in patients treated with NRT, better-educated and more motivated. False expectations, side effects and price can influence adherence to therapy. The smoking habits of the household and the degree of dependency negatively affect adherence and abstinence.

**P1071**
Tobacco cessation quit line in Iran. Evidence based during one year.

**Aim:** To compare the effectiveness of different approaches for smoking cessation: acupuncture and combination of acupuncture and nicotine substituting therapy.

**Methods:** We use two main approaches - acupuncture and combination of acupunc-ture points with NRT therapy. Participants were divided into two groups of 25 people each. The participants who stopped smoking was 21.8% after 2 years.

**Conclusion:** The use of e-Cigarette substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit.

**P1075**
Acupuncture versus combined acupuncture and nicotine substituting therapy for the treatment of nicotineism

**Aim:** To compare the effectiveness of two different approaches for smoking cessation: acupuncture and combination of nicotine and cigarette substituting therapy.

**Methods:** We use two main approaches - acupuncture and combination of acupuncture and nicotine substituting therapy with Tabex (Cytisine, original Bulgarian product). The patients, 50 active smokers (mean age 45 years), highly motivated in smoking cessation, were divided into two groups of 25 people each. The participants in both groups had mean 25 years of smoking history and mean use of 20 cigarettes daily. Acupuncture was performed with standard and micro needles on acupunctural ear and nose points. Tabex was adminstered for 20 days, according to the following regimen: 1 tablet is sucked out in the morning, 1 tablet orally at 10th day, 20th day, 3rd and 6th month after onset.

The results showed that the combined method (acupuncture+Tabex) has more significant long lasting effect (depletion or significant reduction of abstinence, and smoking cessation in 65% of the mild and heavily nicotine dependent patients) at the end of the 6th month than the acupuncture separately (32%).

In conclusion we recommend the combined method of acupuncture and cigarette substituting therapy with Tabex for the treatment of mild and heavily nicotine dependent smokers.

**P1104**
Effect of an electronic cigarette on smoking cessation and reduction: A prospective pilot study

**Aim and objectives:** We designed a prospective proof of concept study to monitor possible modifications in the smoking habits of 40 regular smokers experimenting the most popular marketed e-Cigarette in Italy (Categoria) focusing on smoking reduction and smoking abstinence.

**Methods:** Study participants were invited to attend a total of 5 study visits: at baseline, week 4, week 8, week 12 and week 24. Product use, number of cigarettes smoked, and exhaled carbon monoxide levels were measured at each visit. Smoking reduction and abstinence rates were calculated.

**Results:** A mean of 2.0 cartridges/day was used at week-24. Sustained 50% reduction in the number of cig/day at week-24 was observed in 3/40 (32.5%) participants; their median of 25 cigs/day decreased to 6 cigs/day (p<0.001). Sustained 80% reduction was shown in 5/40 (12.5%) participants; their median 30 cigs/day decreased to 3 cigs/day (p=0.043). Sustained smoking abstinence at week-24 was observed in 9/40 (22.5%) participants. Mouth (20.6%) and throat (32.4%) irritation, and dry cough (32.4%) were common, but diminished substantially by week-24. Participants’ acceptance and acceptance of the product was good.

**Conclusion:** The use of e-Cigarette substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit.
P1076

The impact of education to healthcare professionals (HCPs) on smoking cessation in changing patient referral patterns

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Background: NICE (UK) recommends that every smoker should be advised to quit and referred to a smoking cessation service (SCS) for support. In a previous survey [1], 74% of patients had a missed opportunity for referral to SCS. The current survey evaluates the impact of a HCP education programme on referral patterns.

Method: HCPs including doctors, nurses and pharmacists completed an anonymous, voluntary questionnaire in January 2011.

Results: 58/65 HCPs completed the survey. 45% were aware of local smoking cessation guidelines. 50% had received information on smoking cessation in the last 12 months. 24% did not wish to receive training. 95% evaluated smoking cessation to be important, but only 79% considered that a hospitalization was a useful opportunity to stop smoking. Education by SCS did not alter the reasons given for not referring patients for smoking cessation [Fig 1] of HCPs, although awareness of, and referral to, SCS was higher in the group of HCPs who received education (64% vs 54%). 12% of respondents indicated that referring to SCS was not part of their role.

Conclusion: Education of HCPs did not alter overall attitudes towards smoking cessation in this group, but did result in increased awareness and positively influenced referral rate to the SCS.

References:

P1077

Lung age in smokers – To tell or not to tell?

Kenji Miyamoto, Masayo Takase. Pneumologie, Pavlov State Medical University, Saint-Petersburg, Russian Federation

For smokers, lung age is a useful tool to make spirometry data easier to understand and to increase or maintain the motivation to quit smoking. However, only a quarter of smokers develop COPD. This suggests that many smokers are nonresponsive to tobacco smoking so far as the age-related decline in FEV1 is concerned. Many such smokers might have a lung age younger than their chronological age. We wondered whether, if the lung age is younger than the calendar age, knowing the younger lung age might encourage them to continue smoking.

Purpose: To compare smokers and nonsmokers whose lung ages were younger than their chronological ages when both have normal lung function with no respiratory symptoms.

Subject and methods: We performed spirometry for 353 volunteers who attended our “Lung Age Project” at the University Campus Festival.

Results: Among the subjects, 331 (M/F=158/173) of them had normal spirometry data (80%≤VC and 70%≤FEV1/FVC). In males, 25% of 48 smokers and the same percentage of 110 nonsmokers had a lung age younger than the chronological age. In contrast, in females, 71% of 24 smokers and 46% of 149 nonsmokers had a younger lung age. However, after age and height were matched between both groups, there was no significant difference of the ratio of those who had younger lung age between smokers and nonsmokers, 32% vs. 35% in males and 71% vs. 58% in females, respectively. After telling smokers their younger lung age, some of them happily said “I can continue to smoke for a while”, or “It is too early to quit smoking”.

Conclusion: Many nonsymptomatic smokers have a younger lung age than their chronological age, like nonsmokers. Therefore, we should be cautious about telling lung age to those smokers who want to quit smoking.

P1078

The influence of anxiety on smoking behaviour in patients with chronic hepatitis

José Marínucu, Lucian Negutniu, Stefan Mihaiucu, Ioan Iacobiciu, Nicoleta Bertici, Carmen Ardelen, Ioana Todir, Adriana Neghina, Cristian Oancea, Stefan Frent, Raul Neghina. Clinic of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Clinic of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Clinic of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Clinic of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania Department of Psychology and Educational Sciences, December 1918 University, Alba Julia, Romania Clinic of Infectious Diseases, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Department of Parasitology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

Objective: The study included 68 smokers with chronic hepatitis admitted to the Clinic of Infectious Diseases, Timisoara who answered the State Trait Anxiety Inventory-X2 (S.T.A.I-X2) anonymous test. The final scores allowed classification of patients by level of anxiety: minimal (score below 40), moderate (score 40-60) and severe (score over 60). Other variables were: sex, marital status, residence, number of cigarettes/day, family conflicts, alcohol intake etc.

Results: Most of the patients were male (63.2%, p=0.05). Of the study group, 63.7% had severe anxiety and 35.3% moderate anxiety (p=0.001). The number of cigarettes smoked/day ranged between 10-20 in 73.5% of cases whereas 26.5% of patients reported less than 10 cigarettes smoked/day (p<0.0001); the former group included 44 patients with severe anxiety and 6 cases with moderate anxiety. Patients who increased the number of cigarettes smoked/day after finding out the diagnosis predominated within the study group (67.6%) while only 32.4% of cases smoked less (p<0.0001). Most of the patients reported a positive history of familial conflicts (70.6%, p<0.0001) and alcohol intake (66.2%, p=0.0003).

Conclusions: Considering that severe anxiety in patients with chronic hepatitis leads to an increased number of cigarettes smoked/day, it becomes mandatory to establish a cognitive-behavioral therapy with anti-smoking counseling in these cases.

P1079

Influence of smoking intensity and smoking quitting on lung function parameters in COPD patients

Irina Pavlenko, Julia Ilkovich, Nina Sklarevich. Research Institute of Pulmonology, Pavlov State Medical University, Saint-Petersburg, Russian Federation

Aim: To evaluate dependence of changes in lung function parameters (LFP) from intensity of smoking in patients with moderate and severe COPD.

Materials, methods: 74 patients (63 male, 11 female) with COPD III-IV stages, FEV1 ≤ 0.70, FEV1/FVC% ≤ 50% and FEV1/FVC ≤ 70% were included in the study. Each patient was divided to 2 subgroups: low smoking intensity (less than 20 cigarettes per day) and high smoking intensity (20 and more cigarettes per day). LFP (FEV1 in liters, FEV1/FVC% of pred., “Lung Age” - LA) were measured in both subgroups. Smoking status - 31 current smokers, 33 ex-smokers vs. current smokers in subgroups with high intensity of smoking. Smoking status - 31 current smokers, 33 ex-smokers vs. current smokers in subgroups with low smoking intensity.

Results: LFP significantly improved in a year in ex-smokers vs. current smokers (p<0.05) in all groups. FEV1/FVC% significantly increased in ex-smokers vs. current smokers in subgroups with high intensity of smoking. FEV1/FVC% and FEV1/FVC significantly increased in ex-smokers vs. current smokers in subgroups with low smoking intensity. Other variables were: sex, marital status, residence, number of cigarettes/day, family conflicts, alcohol intake etc.

Conclusions: Smoking cessation has positive influence on lung function parameters in patients with severe and moderate COPD irrespective of smoking intensity. FEV1 in lites is the most sensitive indicator reacting on smoking intensity.

P1080

Evaluation of the antismoking therapy within two specialized medical practice – Arges county

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Objective: Evaluation of the abstinence rate for 1956 people who were administered pharmaceutical treatment combined with psychological support within the
P1081 Behaviour of long-term weight following smoking cessation
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1Clinical of Pulmonary Medicine and Respiratory Cell Research, University Hospital of Basel, Basel, Switzerland; 2Industrial Health Service, F Hoffmann-La Roche AG, Basel, Switzerland; 3Industrial Health Service, Novartis Pharma AG, Basel, Switzerland

Weight gain often accompanies smoking cessation and is considered to be an important cause of unsuccessful quit attempts. We analyzed data from smoking cessation programs to identify risk factors of weight gain. 703 employees from University Hospital Basel, Switzerland, and two local health industry companies (Novartis Pharma AG, F Hoffmann-La Roche AG) absolved a structured smoking cessation program. This consisted of 10 visits with counseling and motivational support. Various modalities of both nicotine replacement therapy and/or bupropion were offered. The impact of factors on weight gain in long-term nicotine abstinence was analyzed by a linear mixed effect model. Smoking cessation at 24 months was associated with a weight gain of 2.76 kilogram (95% CI 1.85; 3.66; p=0.0001). Weight gain occurred independently from smoking cessation program to identify risk factors of weight gain.

Weight change after a quit attempt was not only affected by the outcome of smoking cessation, but also by baseline weight and the interaction of time and medication. Knowledge about individual risk factors for weight gain could help to resolve barriers to cessation smoking.

P1082 Tobacco smoke is a major source of indoor air pollution in Hungary's hospitality venues
Adam Domonkos Tamoki1, David Laszlo Tarnoki1, Mark J. Travers2, Andrew Hyland3, Katherine Dobson2, Laszlo Mechtler3, Ildiko Horvath4, Andrew Hyland2, Katherine Dobson2, Laszlo Mechtler3, Ildiko Horvath4, Anja Meyer1, Daiana Stolz1.
1Clinical of Pulmonary Medicine and Respiratory Cell Research, University Hospital of Basel, Basel, Switzerland; 2Industrial Health Service, F Hoffmann-La Roche AG, Basel, Switzerland; 3Industrial Health Service, Novartis Pharma AG, Basel, Switzerland

Tobacco smoke is a major source of indoor air pollution in Hungary's hospitality venues. Tobacco smoke is a major source of indoor air pollution in Hungary's hospitality venues. Tobacco smoke is a major source of indoor air pollution in Hungary's hospitality venues. Tobacco smoke is a major source of indoor air pollution in Hungary's hospitality venues.

Results: The TSI SidePak AM510 Personal Aerosol Monitor was used to measure the concentration of particulate matter less than 2.5 microns in diameter (PM2.5) measured in the ambient air of 6 public restaurants, 11 cafes and 21 other locations in Budapest and Zala karos between January and August 2008. Results: In the 27 places where smoking was observed the average PM2.5 level was 97.44 μg/m3 [range: 3.48-28 μg/m3] compared to 5.5 μg/m3 [range: 0.28-28 μg/m3] in the 16 places where smoking was not observed. Conclusions: The levels of indoor fine particle air pollution measured in public locations in Hungary where smoking was observed were times higher than the levels in locations where smoking was not observed and in nearly all instances exceeded the levels that the World Health Organization and US Environmental Protection Agency have concluded to be harmful to human health.

P1083 The tenth year preliminary results of smoking cessation polyclinics of Karadeniz Technical University medicine faculty
Funda Ortun1, Gunes Qadri2, Aykut3, Tuvik4, Ismail Yilmaz4, 1Chest Diseases, Karadeniz; Technical University, Medical School, Trabzon, Turkey; 2Public Health, Karadeniz; Technical University, Medical School, Trabzon, Turkey

Aim: Our outpatient smoking cessation clinic was opened in April 2000. Aim of this study was to create a database for our national long-term smoking cessation rates and to share our experience.

Method: We included 696 patients who had applied our smoking cessation clinic between April 2000-December 2010 years. After smoking habits and sociodemographic features of the people were asked, all the people attended to a suitable smoking cessation program. The results were analyzed by Chi-square test, Kaplan Meier survival analysis and Cox-regression analysis.

Results: It was observed that 696 people containing 408 (58.6%) men and 282 (40.5%) women visited the polyclinic during this period. According to duration without smoking, women did not smoke 24.36±6.83 months and men did not smoke 21.63±4.66 months. Success rates were not different between men and women (Log Rank p=0.729) at the end of tenth years. The success rates at the end of the first, the fifth and tenth years in patients who attended smoking cessation program were 58%, 40.6% and 31.7% respectively. We found that male gender, lack of regular income, low education level and the amount of cigarettes smoked per day were independent risk factors for restart smoking by Cox-regression analysis.

Discussion: In conclusion, our smoking cessation rates have decreased over the years. Especially, male gender, low educational level, lack of regular income and high amounts of daily cigarette were reduced success rates. We think that more close follow-up of these patients might positively affect on the success rates.

P1084 Smoking behavior of hospital staff
Yili VakefaII, Jul Bushi1, Dhmiraq Pritfi3, Ibruna Sokoli1, Josif Laçka4, Dhmiraq Arjeti1, Perlat Kapsys1, 1Pneumology, University Hospital “Sh. Ndreoi”, Tirana, Albania; 2Pneumology, Hospital of Pogradec, Pogradec, Albania; 3Pneumology, Hospital of Shkodra, Shkodra, Albania; 4Pneumology, Hospital of Berat, Berat, Albania

Aim: Evaluation of preventive actions at hospital and to measure the implication level of the hospital staff in tobacco prevention.

Method: From 658 hospital staff, 629 (95.6%) were in working place in the time of study, 573 (91.1%) have fulfilled the questionnaire in correctly manner. The questionnaire was articulated in the group questions, the aim of which was to explore the behavior of hospital staff and the level of their perception related to the "tobacco" problem.

Results: 22.5% of the hospital staff smoke, 6.2% smoke in presence of their patients, where the physicians make up the higher percentage (10.2%), in comparison for other healthcare workers (sanitary 5.6% and nurses 3.2%). 82.5% think that trying to convince people to stop smoking is part of their role; 90.2% consider that it has an exemplary role to play in front of patients. 93.4% have the right knowledge according to the damage of tobacco active use. Regarding to "World Day Without Tobacco" 66.1% thinks that this day is useful to rise the susceptibility on the problems related with tobacco using, 25% thinks that this day can help in making mindful the tobacco smoking people to leave it, 8.9% it is useless.

Conclusion: This underlines the need and the necessity to realize anti-tobacco campaigns among health care population. Moreover since the exemplary role they have to play, is very well accepted, preventive actions could rely on a good level of participation.

P1085 Smoking habit – Still a problem in workplace
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Despite the media effort to aware the population on dangerous effect of smoking on health and the laws prohibiting the smoking in workplaces still exist a lack in understanding and applying them.

Aim: To estimate the prevalence of smoking habit, smoker profile in workplace.

Method: Epidemiological study of prevalence;

Study population: 471 workers known to exposure to gas, fumes and mineral dust, aged between 25-65 years. The data were collected on basis of occupational and smoking history, self reported occupational exposure and nicotine dependence test.

Results: Medium age was about 40.6±7 years; 89,1% males. History of exposure: in 54,1% more than 20 years; high exposure in 48%.

194s
Prevalence of symptoms of chronic bronchitis in Murmansk, Russia

Also of smoking on the lung function.

in Soligorsk Central Hospital. The presumably positive effect of potash mine exemplify; 16% recognized the risk of smoking. Nicotinic dependence: extremely 72,2% from workers knew that smoking is harmful but only 26,6% knew to smoking influence on lung function characteristics of potash miners

Objective: Smoking habit: Prevalence, attitudes and behaviour among medical students in Casablanca in 2010

The aim of this study was to know the prevalence of smoking in medical students, and by the way to sensitize the habit and to know their attitudes and behaviour in their future exercise. We carried out a cross-sectional survey from February to March 2010 among 736 medical students enrolled in the university of Medicine and Pharmacy of Casablanca during the academic year 2009–2010. Ninety seven percent of students answered the questionnaire: 61.5% were female 61.5%, mean age 21 years. The prevalence of permanent or occasional smoking was 8% with little variation according to the study year. Smoking was significantly higher among male (16% versus 2.7% in female). The mean daily consumption of cigarettes was 8. The duration of smoking was 6 months or more for 82% and 70% of smokers were slightly or not addicted to nicotine according to the FAGERSTROM’s scale. More than half of the students (58%) had already tried to quit and 52% plan to do so within 5 years. The main triggering reason for quitting was the occurrence of symptoms (66%). Most students knew that smoking is harmful to health (92%). Among tobacco risks the respiratory ones were the best known. Only 39% of the students contemplate to systematically warn their smoking patients against tobacco’s risks. Majority of them (71%) were not aware about the existence of an antitobacco law. But they called for a ban on selling tobacco to children as well as training health workers to help smoking patients to quit. In comparison with some years ago, there is a significant decrease in smoking habit in medical students, may be thanks to a steady and continuing educational effort since the induction of a teaching program in 1983.

P1010
Smoking influence on lung function characteristics of potash miners

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There are known negative effects of smoking on the lung function. The impact of smoking on the lung function of the potash mines with different industrial work record of service has not been so far well investigated.

Objective: The influence of smoking on lung function characteristics of the miners potash mines with different industrial work record of service.

Methods: We examined 111 miners of potash mine in Soligorsk (all male, average age 33.7±11.3 years) with different industrial work record by spirometry: 1 gr. with the record of service less than 10 yrs, II gr. has the record of service from 10 to 20 yrs, and III gr. – more than 20 yrs. 74% of examined miners were smokers. Period of smoking was in average 1.3 year more than industrial work record of service.

Results: The miner’s lung function characteristics were in total very high and according to the normal significance. In I gr. of miners the lung function characteristics were equal to characteristics of smokers and nonsmokers. There were no significant differences in characteristics between the smokers and nonsmokers

Conclusion: Our investigation shows that smoking exerts more intensive negative influence on the lung function of the potash mine workers than industrial aerosols. Antismoking programs could be one of the main points of prophylactic strategy in Soligorsk Central Hospital. The presumably positive effect of potash mine microclimate neutralizes the negative impact not only of industrial aerosols but also of smoking on the lung function.

P1017
Prevalence of symptoms of chronic bronchitis in Murmansk, Russia

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Incidence, morbidity and mortality of COPD in the Murmansk region of northwest Russia are high, but statistical figures do not probably reflect the whole problem. As much as 60% of the male population in Russia is smokers. We describe findings of a project which addresses prevention of COPD in Murmansk.

Aims and objectives: 1. What is the proportion of prolonged respiratory symptoms among adult subjects who visit a GP for primary care?

2. What is the distribution of nicotine-dependence among smokers?

3. How motivated they are to quit smoking?

Methods: A survey of 200 Murmansk region adult citizens was performed. Inclusion criteria: adult patient visiting a primary care GP for any medical reason. Venues were one polyclinic located in Murmansk city and one hospital polyclinic located in a mining area 200 km outside Murmansk.

Results: 200 outpatients were enrolled. Altogether 60.5% had symptoms of chronic bronchitis and 55 (33.0%) had prolonged dyspnoea and wheezing as well. Respiratory symptoms were more common in those subjects, who lived in the mining area. More than half (51.5%) of the subjects had been smokers at some stage of their adult life. A total of 63 (31.5%) were current smokers. The proportion of heavily dependent smokers (FTND 6-7) was 23.8%. Adults living in the mining area were more heavily nicotine dependent. 42.9% of the current smokers had a high motivation to quit smoking.

Conclusions: Significant numbers of primary care patients in Murmansk, Russia experience prolonged respiratory symptoms. Smoking is common in this northern city and there is an urgent need to identify efficient ways for smoking cessation. This study reveals that several smokers have high motivation to quit smoking.

P1086
Smoking influence on lung function characteristics of potash miners

P1087
Prevalence of symptoms of chronic bronchitis in Murmansk, Russia

P1089
Results in a tobacco consulting room in 2008

Francisco Javier Callejas Gonzalez, Sergio Garcia Castillo, Javier Cruz Ruiz, Marila Silvana Plenc Ziegler, Raúl Gódey Mayoral, Ana Isabel Torero Molina, Jesus Jimenez Lopez, Rafaela Sánchez Simon-Talero, Ana Nunez Ares, Fernando Munoz Rino. Pulmonology, University Hospital Albacete, Albacete, Spain

Material and methods: Retrospective descriptive analysis of the results obtained from patients who were attended in a Tobacco Consulting Room from 1 January to 31 December 2008 and subsequent follow-up to complete a year.

108. Smoking rate: smoking cessation interventions
Results: 268 of 410 patients (56.3% male), mean age 46 years and mean cigarettes/day 27.1. Statistical significance between cigarettes smoked and sex, higher in males. Respiratory comorbidity: 15.7% COPD, 9% asthma, 10.8% OSAHS and 1% OCD. Cardiovascular comorbidity, 7.83%, and psychiatric, 32.46% 44.4% without treatment, 22.8% NRT, 6.3% bupropion and 26.5% varenicline. Overall of the 268 patients, treatment success in 45 (16.8%), 29 men and 16 women. Percentage rises to 29.6% if we don’t consider those who didn’t attend the second consultation. Success among respiratory patients was statistically significantly longer compared with cardiac (27.1% vs. 4.7%, p < 0.03) and among non-psychiatric compared with psychiatric ones (19.8% vs. 10.3%, p < 0.05). Those who were treated pharmacologically, statistically significantly greater success among who used varenicline than NRT or bupropion (35.2% vs. 21.5%, p < 0.001).

Conclusions: 1. 62.92% didn’t start treatment (34.64% and 28.28%, first and second appointment respectively). 2. Cigarette consumption by males was significantly higher than women (28.51 vs. 25.08, p < 0.02). 3. Overall treatment success 16.8%, amounting to 29.6% excluding those who don’t attend the second consultation. 4. Greater success among respiratory than cardiac patients (27.1% vs. 4.7%) and among non-psychiatric than psychiatric ones (19.8% vs. 10.3%). 5. Greater success among varenicline than NRT or bupropion-treated (35.2% vs. 21.5%).

P1091 Special characteristics of smoking cessation program participants in a large municipal hospital in Greece

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Introduction: Greece is the European Union country with the highest rate of tobacco consumption (more than 40%) enforcement of laws forbidding consumption of tobacco products, combined with public awareness of the adverse effects of smoking, result in the need for efficient smoking cessation centers.

Aims: The aim of the present study is to demonstrate special characteristics of smokers addressing to the smoking cessation center of Evangelismos hospital, in Athens Greece, including dependence, motivation profile, special characteristics such as depression profile and pulmonary function testing values.

Methods: Three hundred (300) smokers of mean age of 48.74±11.42 years, smoking 38.97±22.87 packyears participated in Evangelismos Hospital smoking cessation program during the last two years. A thorough medical history was obtained focusing on dependence and motivation for quitting.Pulmonary function testing, including spirometry was performed in all individuals. Statistical analysis was performed using the non-parametric test for sign values.

Results: Men smoke more than women (47.52±26.61 vs 35.33±22.05). One the other hand Greek women present more motivated to quit smoking than men (16.26±11.32 vs 10.08±12.08).In addition pulmonary function testing reveals high percentage of abnormalities caused by smoking, such as small airway disease. Abandoning the cessation program is significantly ralated (p<0.05) with a depressive profile of the participant.

Conclusions: Smoking cessation programs reveal interesting profiles of the Greek population, concerning the smoking habit, pulmonary function testing abnormalities and factors related to abandoning a smoking cessation program.

Objective: To assess what factors are associated with a higher rate of smoking cessation.

Material and methods: Cross-sectional study of a sample of smokers. Of a total of 1545 patients were analyzed those patients on whom information is available smoking within 6 months of follow-up. We defined 2 groups: group 1 who do not attend all visits but answer phone calls to complete a period of 6 months of treatment; group 2, patients attending all follow-up visits.

Results: See table. The results of the quantitative variables are expressed as mean and standard deviation. The results of the qualitative variables are described as the absolute value and percentage.

P1092 Factors associated with smoking cessation in a smoking cessation unit

Carlos Almendariz Sanchez, Ignacio Sanchez Hernandez, Ignacio Sanchez Carrasco, Juan Pablo Rodriguez Gallego, Elizabeth Guzman Robles, Saray Quiros Fernandez, Jesus Fernandez Frances, Jorge Castelo Naval, Jose Luis Izquierdo Alonso. Pulmonary Medicine, Guadalajara University Hospital. Guadalajara, Spain

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P1093 Research of smoking in health workers in Hospital Cacak-Serbia

Nada Ljorovic1, Sladjana Magistorovic2, Julijana Antonovic1, Ika Preic4, Dusko Sulubic4. 1Department for Smoking Cessation, Hospital, Cacak, Serbia; 2Department for Otorhinolaryngology, Hospital, Cacak, Serbia; 3Department for Pulmonology and Th. Hospital, Cacak, Serbia; 4Department for Smoking Cessation, Clinical Centre, Belgrade, Serbia; 5Department for Pulmonary Disease, Medical Centre, Gaca, Serbia

Background: Explore Health inhabitants of Serbia 2006 adult smoking prevalence was 33.6%, exposure to tobacco smoke (TS) in the workplaces is 50%.

Objectives: Quantitative goals of tobacco control strategies predict increase in the number of jobs without the tobacco smoke of 5% a year and reducing exposure to TS in public places for 1% a year.

Methods: We surveyed 462 health workers of 626 total employees in the City Hospital in Cacak: physicians (MD) 115 (24.9%), 326 medical technicians (MT) (70,6%) and other 21 (4.5%); male (M) 90 (19.5%) and female (F) 372 (79.2%).

Results: The average age of employees is 42.6 years. Smokers (S) 218 (47.16%), Non-S 185 (40%), Ex-S 59 (12.84%). Questionary: 1) Do you have: a- complete ban on smoking in the hospital 31.8%, b-smoking separation zone 56.1%, c-free smoking 12.1%. 2) Is smoking: a-risk for the health of 68.8%, b-moderate risk 32.8%.

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Conclusions: 1. 62.92% didn’t start treatment (34.64% and 28.28%, first and second appointment respectively). 2. Cigarette consumption by males was significantly higher than women (28.51 vs. 25.08, p < 0.02). 3. Overall treatment success 16.8%, amounting to 29.6% excluding those who don’t attend the second consultation. 4. Greater success among respiratory than cardiac patients (27.1% vs. 4.7%) and among non-psychiatric than psychiatric ones (19.8% vs. 10.3%). 5. Greater success among varenicline than NRT or bupropion-treated (35.2% vs. 21.5%).

P1094 Abundance of smoking cessation reasons in participants of smoking cessation clinic

Zahra Hessami, Mahshid Aryanpur, Gholamreza Heydari, MohamamadReza Masjedi, Shabnam Esampanah. National Research Institute Tuberculosis and Lung Disease Tobacco Prevention and Control Research Center, Shahid Beheshti University, Tehran, Islamic Republic of Iran

Introduction: Cigarette smoking is an important cause of respiratory and other health problems around the world. Stop Smoking at any age could be decreasing these problems. Smokers finally think about smoking cessation. Having Strong reasons to quit is important factor for attempt to quit.

Objectives: We aimed to investigate what their motivations to quit are?

Method: This cross-sectional study was done on the volunteers of smoking cessation clinic of tobacco prevention and control research center. Data from (345)
Low-income is a predictive factor of failure associated with smoking cessation at a public clinic in Brazil

Rafaela F. Xavier, Dionei Ramos, Giovana N.B. Ferrari, Juliana T. Ito, Fernando M.M. Rodrigues, Alessandra C. Toledo, Ercy M.C. Ramos. Physiotherapy, UNESP - Sao Paulo State University, Presidente Prudente, Sao Paulo, Brazil

Smoking cessation programs (SCP) are the main way to reduce tobacco related mortality and morbidity. The search for predictors of failure or success specific to a population with special characteristics, such as Brazilians, should be the first step in the development of SCP national. We evaluated the demographic characteristics and factors influencing the failure or success of quitting among participants in a SCP. This retrospective study was conducted from 2008-2009 in a SCP based on cognitive behavioral treatment associated or not with medication therapy consisted in 20 meetings during 12 months. After that the individuals were invited to answer a socio-economic questionnaire by telephone. A total of 15% of individuals were included in this study and 65 agreed to answer a socio-economic questionnaire (aged=49±10, pack-years index=35±24, women=63%). Regarding education level: 50% had primary education, 29% had high school and 21% had university education. According with sociodemographic questionnaire 14% of the individuals were at class A2, 21% at class B2, 54% at class C1 and 11% at class D. After the fourth meeting 47.7% of individuals attempt to quit but only 32% of this professional aid in smoking cessation intervention in national programs.

Knowledge about tobacco according to smoking habit and level of formal education

Paulo Gregorio, Bruno Lemos, Aline Moraes, Felipe Mattos, Marina Sampayo, Priscila Viveiros, Ierna de Godoy. Clinical Medicine, Botucatu Medical School, Botucatu, Sao Paulo, Brazil

Tobacco related illnesses are important public health issues worldwide. Population’s knowledge about smoking and awareness about health risks are keys for cessation. We aimed to analyze the knowledge about tobacco and how this is influenced by smoking habit and level of formal education. We interviewed citizens who took part in an event of preventive health in a town of the State of Sao Paulo, Brazil. We interviewed 190 subjects, with age 49.5 ± 18y, 59% males, 26.3% smokers, 49% non-smokers and 24.7% former smokers. A standard questionnaire was applied with the following main questions: 1) Is tobacco dependence a disease?; 2) Is low level of consumption safe?; 3) Do you receive any information about smoking cessation?; 4) Is tobacco a disease?; 5) Do you want to stop smoking? A total of 87% of the subjects interviewed received some kind of information about their health. However, 27% of them did not consider smoking a disease and 32% considered that a low level of smoking would not represent a danger or risk to their health.

In conclusion, the percentage of smokers in our sample is consistent with the prevalence of tobacco smoking in our country. The percentage of former smokers reflects the impact of Brazilian policies for tobacco control. Although anti-smoking campaign are designed to reach all social layers through an accessible language, we find that the knowledge about tobacco are still incomplete among general population.

Smoking prevalence and smoking behaviour among Portuguese physicians: A cross-sectional study

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Background: Studies evaluating Portuguese physicians’ smoking behaviour are limited and applied different methodologies. Studies from the 70’s and 80’s show high prevalence rates, higher than the general population. Recent studies had reported decreasing smoking prevalence trends. However, it is not clear if physicians are smoking less than the general population and whether this decreasing trend has continued thereafter. In 2009, a survey was carried out to evaluate smoking prevalence trends and smoking behaviour among Portuguese physicians.

Methods: Questionnaire-based cross-sectional study, conducted during two main national medical conferences, using a convenience-sample methodology. Physician smoking behaviour was self-reported.

Results: Participants: 607 physicians; 57.6% primary care; 33.1% hospital-based specialists; 9.3% undergraduate students; 62.7% females; median age 34. Smoking prevalence was 29.6% in males, 15.3% in females (p < 0.001). Smoking prevalence was not related to medical specialty; 53.3% of the smokers reported being daily smokers, smoking in average 10 cigarettes a day; median of regular smoking age was 18 years. 46% of the smokers reported desire to stop smoking, 56.7% had already tried to quit but only 33.8% reported needing assistance on their quit attempt. Age-gender specific analyses revealed that the majority of younger physicians (aged≤44) reported being never smokers (males: 62.7%; females: 77.6%), in contrast to older smokers (p < 0.001).

Conclusions: Smoking prevalence among Portuguese physicians is decreasing and is lower than in general population. Physicians smoke less cigarettes and reported more occasional smoking than the general population.
Smoking cessation is associated with substantial health benefits. Nevertheless out-
coming of smoking cessation was often investigated on strongly selected populations.
We aimed to assess the influence of our smoking cessation programme on lung function under real life conditions.

703 smoking employees from University Hospital Basel, Switzerland, and two local health industry companies (Novartis Pharma AG, Hoffmann-La Roche AG) participated on a structured smoking cessation programme. The programme consisted of 10 visits with counselling and motivational support within 2 years of follow-up. Various modalities of both nicotine replacement therapy and/or bupro-

P1102 Exhaled carbon monoxide according to daily cigarette consumption in
healthy smokers
Juliana Zabatore1, Demétria Kovelis1, Mahara Pronça1, Karina Furlanetto1, Leandro Camões2, Filoñ Pinto1, Gabriela de Aquino em Fisioterapia Pulmonar (LFPF), Universidade Estadual de Londrina (UEL), Londrina, Brazil; 2Programa de Mestrado em Fisioterapia, Universidade Estadual Paulista Julio de Mesquita Filho (UNESP), Presidente Prudente, Brazil

Methods: To compare the exhaled carbon monoxide (CO) levels in apparently healthy smokers according to the intensity of cigarette consumption and verify its relationship with lung function and nicotine dependence.

Methods: Forty-four healthy smokers (20 male, 48±12 years, BMI: 27.4±4 kg/m²)
were influenced by BMI (p=0.017, β=0.358) and the number of cigarettes smoked per day (p=0.025, β=0.398). SOD was also negatively influenced by BMI and WC (p<0.05 for both). FEV1 was related negatively with WC (p=0.047, β=0.31).

Conclusion: There is an increased oxidative stress and chronic inflammation in heavy smokers with long smoking history. These processes are closely linked with obesity, which along with smoking increase the risk of early decline in lung function.

P1101 Active smoking negatively affects recovery of patients hospitalized due to
acute exacerbation of chronic obstructive pulmonary disease (COPD)
Andrea Schäfer, Noémi Eszes, Zsuzsanna Kováts, Veronika Mülter. Pulmonology, Semmelweis University, Budapest, Hungary

COPD is a progressive inflammatory airway disease most often caused by smoking. Significant proportion of COPD patients continues to smoke even in advanced stages, mainly as the result of severe tobacco dependence. COPD predisposes to depression making symptoms worse. Frequency and effects of active smoking and depression in patients hospitalized due to acute exacerbation of COPD is unknown. One hundred patients admitted to the Department of Pulmonology Semmelweis University with the diagnosis of COPD acute exacerbation were analyzed (men: women = 46:54). Detailed history, Fagerström nicotine dependence test (FNDT) and the Beck depression inventory scale were registered, expired CO was mea-

The outcome of a smoking cessation attempt as well as baseline lung function and medication significantly influenced FEV1 within 2 years of a quit attempt. These observations could be important in encouraging smokers to stop smoking.

References:

Results:
Significant correlation of 0.4 with the number of cigarettes smoked in the last 24h (p<0.05). In patients with FEV1<30% predicted, there was no significant decrease of FEV1 at baseline (p=0.056). The changes in FEV1 and in CO levels between G1 and G3 (p=0.013) but not between G1 and G2 (p=0.138). When analyzing the relationship between CO levels of smokers as a whole with smoking habits and nicotine dependence, moderate cor-
relations were found with number of cigarettes smoked in the last 24h (p=0.54, p<0.01), cigarettes/day (p=0.53, p<0.01), FTQ (p=0.33, p=0.02), pack-years (p=0.32, p=0.03) and time since last cigarette smoked (r = 0.31, p<0.04). These relationships were not found when assessing each group separately.

Conclusions: Exhaled CO levels are higher in heavy smokers in comparison to moderate and light smokers, whereas no difference was found between moderate and light smokers. Moreover, CO levels are related with smoking habits and nicotine dependence.

P1103 Effects of paternal tobacco use on different parameters of a newborn child
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Introduction: There has been significant research done on the effects of maternal smoking on pregnancy but not much data is available regarding the role of paternal smoking and its effect on the vitals of a newborn child. We therefore tried to evaluate the effects of paternal tobacco use on newborn child.

Methods: A prospective study carried out in gynecology and obstetrics department of our hospital. A questionnaire based interview was conducted with the delivering females in the month of October 2010 in terms of tobacco use of their spouse during pregnancy. The neonatal vitals were assessed and previous abortion history was also inquired.

Results: Age of the delivering females was 28.34 years ±4.095 S.D. Females delivered was n=100. Tobacco use was found among spouses of n=25 females. Out of them n=14 were smokers and n=13 chewed tobacco whose husbands smoked (n=14) previous abortion history was found in n=6 (42.85%) females out of which n=2 females were exposed to tobacco smoke during those earlier pregnancies, as compared to females with non smoking husbands (n=38) previous abortion was noted in n=19 (20.09%). Among females whose husbands chewed tobacco (n=11) previous abortion history was found in n=3 females. Among n=2 preterm neonates n=1 had paternal smoking history. Of n=7 neonates with respiratory distress n=2 had paternal smoking history, n=1 (out of n=2) had delayed sucking and n=1 had delayed micturition.

Conclusions: Our results suggest that paternal tobacco consumption might have risks to the newborn child & ongoing pregnancy. Paternal smoking may have biological correlation with such outcomes. Further research should be carried out in this aspect.

P1104 Smoking cessation in tuberculosis and COPD patients
N.V. Yahorava, H.L. Hurvech, A.A. Ringa, M.A. Skrahna, T.M. Krytskaia. Clinical, RSFC for Pulmonology and Tuberculosis, Minsk, Belarus

The aim of this study was to investigate clinical, nicotine dependence status in smoking tuberculosis (TB) and COPD pts, efficacy of treatment of nicotine depen-
dence by nicotine acetylcholine receptor agonist (cytine), mexidol, behavioural intervention in TB and COPD pts.

Methods: 91 smoking TB and COPD pts (74m, 17w, age 41±8) were examined before and after 3 months of treatment. 50 Pts have been treated with 4-5 anti-
tuberculosis drugs, basic course of COPD (82-agonist, anticholinergic, corticoids, 02), cytine (1.5-5mg/dag-25days), mexidol (100mg/dag-25days), behavioursal intervention. 41 Pts have received 4-5 antibacterial drugs and basic course of COPD only (Gr2). Examination of clinical status, blood gases, pulmonary function tests, quiz pts about their smoking status had been performed in all pts.

Results: In TB and COPD pts was found low nicotine dependence, low moti-
vation to quit. After 3 months of treatment in TB and COPD pts clinical status was improved. Smoking cessation was achieved in 16% pts of Gr1, decrease of nicotine consumption-60% pts of Gr1. In 76% pts of Gr1, 71% pts of Gr2 was found improvement of chest X-ray. Sputum conversion was found in 80% pts of Gr1, 73% pts of Gr2. In Gr1 was found increase of forced expiratory volume in 1 second for predicted on 14%, p<0.05, peak expiratory flow for predicted on 13%, p<0.05, decrease of PCO2 on 14%, p<0.01, HCO3- on 8%, p<0.05. In COPD pts changes were not found.

Conclusions: In TB and COPD pts treatment of smoking, mexidol, behavioural inter-
tervention to antibacterial and basic course of COPD leads to decrease of level
of nicotine consumption, improvement of clinical, blood gases exchange status, pulmonary function.

P1105
Association between dopamine transporter, monoamine oxidases genotypes and tobacco smoking
Marina Smirnova1, Natalia Mitushkina2, Olga Suhovskaya1, Evgeniy Imyanitov1, 2
1Palmolivia, State Medical University, St. Petersburg, Russian Federation; 2Oncology, N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation

There are many polymorphisms of genes involved in metabolism of compounds contained in tobacco smoke (MAOA, MAOB, DATI and DRD2). Dopamine (DA) is critical for reward and its predictive signals, genetically driven variation in DA transmission may account for the observed differences.

The aim of study was to examine interactions between DATI and MAOA polymorphisms and nicotine dependence, number of cigarettes and successful quit smoking in healthy smokers, patients with COPD and asthma.

Methods: 99 smokers-males (36-78 years) were genotyped for polymorphisms of DATI, MAOA. CO breath testing has been made for cigarette smokers.

Information about current tobacco consumption was obtained using self-report measures and structured interviews.

Results: Age at initiation of smoking was assessed at age 12 and 22 years. Results suggest that age at onset of intensive consumption and nicotine dependence (ND) moderated the association of the DATI gene. Individuals with DATI 40 bp (6R, 7R, 8R) and DATI 30bp (5R) had lower nicotine dependence and they quit smoking more successful than smokers with DATI 40 bp (10R, 11R) p=0.038 and DATI 30bp (6R, 7R, p=0.029). ND patients with COPD p=2.54±0.36 (from 4 to 10), asthma 3.15±0.44 (from 3 to 8). Patients with COPD more often had DATI 40 bp (10R, 11R) than patients with asthma (p=0.039).

Have been revealed association between the MAOA polymorphism and smoking (p=0.48). Smokers with COPD and smokers with several nicotine withdrawal more often had 3R 4R MAOA.

Conclusion: These results support the hypothesis that the DATI and MAOA polymorphisms are associated with smoking cessation and can influence on smoking cessation in patients with COPD.

P1106
Smoking induced satellite associations in a rural population of south India
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A smoker is exposed to a variety of carcinogenic constituents present in cigarettes, making it essential to analyze the biological effects of these constituents as they may be a health hazard to the future generations1. Cytogenetic assay in peripheral blood lymphocytes was done to assess the incidence of Satellite Associations among 30 smokers and 30 non-smokers in a rural population of South India. Smokers were divided into three groups based on their Smoking Index (SI): I - SI less than 150, II - SI 150 to 300, III - SI more than 300. An equal number of matched control individuals were selected and Lymphocyte cultures were set up from heparinised blood. The mean frequency of satellite association in smokers belonging to group I, II and III were 45 (44.25±3.30), 53 (53±6.34) and 67 (67±6.22) respectively, whereas the mean frequency of satellite association in non-smokers was 29.83% (29.83±6.22) respectively.

The frequency of Satellite Associations in smokers I, II and III increased with the increase in the frequency of their smoking index than their non smoking counterpart. The students 1"t" test (SSP software) for satellite association was found to be highly significant at p ≤ 0.01 in all the three Smoker Group viz. I, II and III.

These findings confirm the genotoxic effect of cigarette smoke on the chromosomes and can be used as a Smoking Cessation Intervention tool.

References:

109. New insights in paediatric respiratory physiology

P1107
Single-breath lung diffusion capacity for carbon monoxide in children and young adults born extremely preterm
Emile Sadath1, Ola Rokhsand2,3, Einar Thoresen1, Thomas Halvorsen1, 2
1Department of Clinical Medicine, University of Bergen, Bergen, Norway; 2Department of Pediatrics, Haukeland University Hospital, Bergen, Norway; 3Institute of Medicine, University of Bergen, Bergen, Norway

Introduction: Extreme preterm (EP) birth is associated with acinar developmental alterations, potentially influencing lung diffusing capacity (DLCO) and gas exchange. Techniques of measurement are complex and feasibility in children needs to be addressed.

Aims: To study repeatability of DLCO in children and young adults, and to compare results of subjects born EP and at term in two different decades.

Methods: Two area-based cohorts of subjects born at gestational age (GA) ≥28 weeks or with birth weight (BW) ≥ 1000 grams in the two periods 1991-1992 (n=35) and 1982-1985 (n=46) and matched controls born at term performed single-breath DLCO tests twice within two weeks. Mean ages (SD) were 10.6 (0.4) and 17.7 (1.2) years.

Results: The coefficient of variation for interession measurements of DLCO for subjects born preterm and at term in the 1991-92 and 1982-85 birth-cohorts were 8.2 and 7.7%, and 9.5 and 7.6%, respectively. EP birth was associated with significantly reduced height adjusted DLCO and with lower KCO**. Deficits were similar in the two birth-cohorts (test of interaction, p = 0.410).

P1108
Effect of prenatal exposure to tobacco on lung function of infants born preterm
Manuel Sanchez-Solis1,2, Luis Garcia-Marcos1,2, Virginia Perez3, Pedro Mondejar1, Maria Dolores Pastor1
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Introduction: The exposure of fetuses to tobacco during pregnancy, in otherwise healthy infants born at term, is associated to lower expiratory flows as measured both by means of the rapid thoracoabdominal compression technique (RTC) and by the raised-volume rapid thoracoabdominal compression technique (RVRTC).

The aim of the present study is to measure lung function by RVRTC in healthy infants born preterm exposed or non-exposed to tobacco in pregnancy.

Methods: Forced vital capacity (FVC), forced expiratory flows at 50%, 75%, 25-75% of FVC (FEV50, FEV75, FEF57, FEF25-75) and forced expiratory flow at 0.5 sec (FEV50), were obtained by RVRTC. These parameters were compared to controls born at term, at a corrected age of 7 months, without neonatal respiratory distress. A multivariate linear regression analysis adjusted for gender, gestational age, corrected age, length and prenatal tobacco exposure, was performed.

Results:

Table 1. Multivariate regression coefficients of lung function parameters of infants born preterm exposed to tobacco in pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (mL)</td>
<td>-28.75</td>
<td>-55.44, -2.10</td>
</tr>
<tr>
<td>FEV50 (mL)</td>
<td>-20.67</td>
<td>-33.32, 41.98</td>
</tr>
<tr>
<td>FEF75 (mL)</td>
<td>-13.27</td>
<td>-58.22, 31.67</td>
</tr>
<tr>
<td>FEF55 (mL)</td>
<td>-13.23</td>
<td>-52.45, 25.99</td>
</tr>
<tr>
<td>FEF25-75 (mL)</td>
<td>-12.27</td>
<td>-74.56, 50.02</td>
</tr>
<tr>
<td>FEV0.5 (mL)</td>
<td>-3.90</td>
<td>-34.10, 26.30</td>
</tr>
<tr>
<td>FEV0.5/FVC</td>
<td>0.08</td>
<td>-0.167, 0.346</td>
</tr>
</tbody>
</table>

Table 2. Multivariate regression coefficients of lung function parameters of infants born preterm exposed to tobacco in pregnancy

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (mL)</td>
<td>-28.75, -2.10</td>
</tr>
<tr>
<td>FEV50 (mL)</td>
<td>-20.67, 41.98</td>
</tr>
<tr>
<td>FEF75 (mL)</td>
<td>-13.27, 31.67</td>
</tr>
<tr>
<td>FEF55 (mL)</td>
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</tr>
<tr>
<td>FEF25-75 (mL)</td>
<td>-12.27</td>
</tr>
<tr>
<td>FEV0.5 (mL)</td>
<td>-3.90, 26.30</td>
</tr>
<tr>
<td>FEV0.5/FVC</td>
<td>0.08, 0.346</td>
</tr>
</tbody>
</table>

Conclusions: Infections born preterm, at a corrected age of ~7 months, prenatal tobacco exposure is significantly associated to a lower FVC, but does not change forced expiratory flows.

P1109
Acetazolamide for severe hyperventilation and apnea in a child with Pitt-Hopkins syndrome
Stijn Verbout1, Wilfried De Backer2
1Pediatrics, University of Antwerp, Wilrijk, Belgium; 2Respiratory Medicine, University of Antwerp, Wilrijk, Belgium

Case report: We present the case of a 9 year old boy with Pitt-Hopkins syndrome...
In view of the hyperventilation, we started the patient on 250 mg of acetazolamide once daily. The patient was reevaluated one and a half month later. The clinical picture was markedly improved: long lasting apneas and episodes of syncope were no longer observed. A blood gas showed a pH of 7.35 with a pCO2 of 32.9 mmHg and a base excess of -6.5 mmol/L. Polygraphic monitoring showed the presence of several short central apneas but with preserved oxygen saturation and a more stable CO2 curve.

Discussion: Pts-Hopkins syndrome is due to de novo mutations at the TCF4 locus and is characterised by distinct facial features, mental retardation and episodic hyperventilation with apnea while awake. Both the pathogenesis of these hyperventilation episodes as its treatment are unknown. This is the first report on the positive effect of acetazolamide on daytime hyperventilation and apnea in this syndrome. In this view; it would also be interesting to study the effects of acetazolamide in patients with similar syndromes including Rett and Joubert syndrome.

P1110
Peripheral airway function versus spirometry in childhood asthma
Sanna Kjellberg1, Paul Robinson2, Emilia Viklund1, Maria Strom1, Per Gustafsson1, Department of Paediatrics, Central Hospital, Skövde, Sweden;2Department of Respiratory Medicine, Children’s Hospital at Westmead, Sydney, New South Wales, Australia.

Background: Tests of peripheral airway function are rarely used in clinical studies of paediatric asthma. The relationships between FEV1 and indices of small airway function from inert gas washout and impulse oscillometry have not been directly compared and are largely unknown.

Methods: Scord and Sacin (inert gas indices of ventilation inhomogeneity in the conducting and acinar airway zones, respectively) were measured from mass spectrometer multiple breath SF6 washout. Frequency dependence of resistance (R5-R20Hz, a measure of small airway obstruction) was measured using impulse oscillometry (IOS). Both of these tests were performed prior to spirometry, both at baseline and post-bronchodilatation (BD) (400 mcg salbutamol inhalation) in 58 subjects aged 8-18 yrs with stable asthma of mild to moderate severity. Reference values for Scord and Sacin were obtained from 45 healthy subjects and for R5-R20Hz from 169 age matched controls. Spirometric reference values were taken from Staňojević et al 2009 [1]. Results were expressed as z-scores.

Results: FEV1 was normal (z score > 1.96) in 48/58 (83%) at baseline and 58/58 (100%) subjects post-BD. In those subjects with normal FEV1 abnormal (z score > 1.96) R5-R20Hz, Scord and Sacin were found in 38/48 (79%), 26/47 (55%), and 5/47 (11%) at baseline and 18/58 (31%), 15/56 (27%) and 4/45 (9%) of subjects post BD, respectively.

Conclusions: Peripheral airway dysfunction is common in school age asthmatics with normal FEV1. This abnormality persists in almost a third despite bronchodilatation. The most sensitive indices to detect this peripheral abnormality are R5-R20Hz and Scord.

Reference:

P1111
Vocal cord dysfunction in adolescents
Johannes Schulze, Sarah Weber, Martin Rosewich, Olaf Eickemeyer, Markus Rose, Stefan Zieilen, Department of Allergy, Pulmonology and Cystic Fibrosis, Children’s Hospital, Goethe-University, Frankfurt, Germany.

Background: Vocal cord dysfunction (VCD) often presents with dramatic and abrupt symptoms. To diagnose VCD, visualisation by direct laryngoscopy is required and usually a specific method to provoke VCD is needed.

Objectives: Adolescents with clinical suspicion of VCD were invited to participate. The first objective was to diagnose VCD, second objectives were changes of pulmonary function test (PFT) and predictors of VCD before and after methacholine challenge test (MCT).

Methods: After an initial PFT, a direct laryngoscopy was performed. This was followed by the MCT; the endpoint was the methacholine dose causing a 20% drop of the forced expiratory volume in one second (PD20FEV1). After that a second laryngoscopy was conducted. PFT changes before and after MCT were compared with the data of 14 healthy controls (HC).

Results: Thirty-five patients (8-19 years) were investigated. Three failed to have a significant reaction to methacholine and three showed anatomical alterations. In the remaining 29 patients, 14 had VCD and 15 had bronchial hypersensitiveness (non-VCD). PD20FEV1 methacholine was significant lower in VCD compared with non-VCD (VCD 0.24 mg ± 0.4, non-VCD 0.73 mg ± 0.73; p= 0.001). VCD patients showed significantly lower PFT parameters after MCT; FEV1, VCD 58.5% ± 20.1, non-VCD 77.8% ± 18.4, and HC 98.7% ± 16.6 (p< 0.0001); inspiratory vital capacity (IVC); VCD 61.3% ± 20.9, non-VCD 75.7% ± 14.8, and HC 101.1% ± 15.4 (p< 0.0004).

Conclusions: The combination of MCT and laryngoscopy may be able to differentiate between VCD and non-VCD patients. VCD patients showed a positive reaction at lower methacholine doses and had a higher airway obstruction. PFT and MCT do not replace direct laryngoscopy in the diagnosis of VCD in adolescents.

P1112
Evolution of lung function in preterm infants with or without bronchopulmonary dysplasia
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Introduction: Healthy preterm infants do not catch-up lung function (LF) during the first two years of life. The aim of study is to compare the evolution of LF in infants born preterm, with and without BPD.

Methods: Forced vital capacity (FVC), forced expiratory flows at 50%, 75%, 25-75% of FVC (FEF50, FEF75, FEF25-75) and forced expiratory flow at 0.5 sec (FEF0.5) was obtained by raised volume rapid thoracoabdominal compression technique (RVRTC) in 14 (7 males) BDP+ and in 12 (6 males) infants born preterm BDP-. Measurements were repeated at 6 and 12 moths after baseline. A generalized estimating equations (GEE) adjusted for gestational age, length, corrected age and body mass index z-score (according OMS tables) was built for boys and girls separately.

Results:

Table 1. Characteristics of BPD+

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male Mean (SD)</th>
<th>Female Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>26.6 (1.4)</td>
<td>25.0 (0.8)</td>
<td>0.025</td>
</tr>
<tr>
<td>Neonatal weight (grams)</td>
<td>900 (84.7)</td>
<td>764 (56.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Corrected age 1st measure (months)</td>
<td>4.7 (2.7)</td>
<td>5.4 (3.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Length (z-score)</td>
<td>-1.0 (0.6)</td>
<td>-0.42 (2.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>BMZ (z-score)</td>
<td>-0.69 (1.59)</td>
<td>-1.87 (0.85)</td>
<td>0.12</td>
</tr>
<tr>
<td>Oxygen dependency (days)</td>
<td>70.6 (14.3)</td>
<td>119.9 (81.4)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table 2. GEE coefficients of LF parameters of infants born preterm BDP+ (base: BDP-)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male β 95% IC</th>
<th>Female β 95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (mL)</td>
<td>-76.1, -112.9, -39.3</td>
<td>20.3, -61.2, 101.7</td>
</tr>
<tr>
<td>FEF50 (mL/s)</td>
<td>-60.4, -178.4, 57.5</td>
<td>156.8, 45.3, 228.3</td>
</tr>
<tr>
<td>FEF75 (mL/s)</td>
<td>-53.1, -107.5, 1.31</td>
<td>62.9, -2.4, 124</td>
</tr>
<tr>
<td>FEF25-75 (mL/s)</td>
<td>-59.8, -176.6, -13.1</td>
<td>137.6, 35.6, 239.6</td>
</tr>
<tr>
<td>FEF0.5 (mL/s)</td>
<td>-50.0, -74.8, -25.2</td>
<td>37.9, -7.7, 81.8</td>
</tr>
<tr>
<td>FEV0.5/FVC</td>
<td>-0.02, -0.09, 0.05</td>
<td>0.07, 0.0002, 0.14</td>
</tr>
</tbody>
</table>

Conclusions: FVC, FEF25-75 and FEF0.5 decrease among male infants with BPD as compared to those without BPD; however in female infants they tend to be similar, and FEF50, FEF25-75 and FEV0.5/FVC even improve.
Field test and an ergospirometry with maximal stress on a treadmill and study the correlation between the principle variables of both tests.

Methods: It is a descriptive transversal study carried out amongst obese children from 6 to 14 years old with a control group of normal-weight children. A 6MWTD and an ergospirometry on a treadmill with an incremental maximal stress protocol according to the ERS/ATS recommendations were carried out on the obese children. On the control group, the 6MWTD was carried out.

Results: A total of 28 obese children (17 male, 61% were studied, with an average age of 10.90 years old (±2.43) and a BMI of 27.61 kg/m² (±3.46). The average 6MWD was 539.4 m (±44.6), which makes up 92.94% (+11.27) of the theoretical. The HRmax in the 6MWT was 70.10% (±7.24) of the maximum and the perceived effort scale (PE) was 6.8 (±1.6). The VO2peak was 35.64 ml/kg/min (±5.86), placing itself at 83.21% (±5.86) of the theoretical. The HRmax was 192.84 bpm (±10.10) which makes up 92.05% (+5.17) of the maximum. The RER was 1.15 (±0.13) and the PE was 9.40 (±0.84). The correlation between the 6MWD and the VO2peak was not significant (p=0.05). In the group of normal-weight children, the 6MWD was 95.5% (±7.56) of the theoretical, the HRmax% was 60.75% (±7.96) and the average was 83.21% (±6.13). Significant differences (p<0.05) were found between the PE and the HRmax% reached between the group of normal-weight and the obese children.

Conclusions: The obese children are able to maintain the distance walked in the sub-maximal stress test at the expense of a greater maximal heart rate and a greater stress perception than the normal-weight children.

P1116 Respiratory impedance using forced oscillation technique in preschool children with a history of wheezing

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Background: This study aimed to assess respiratory impedance using the forced oscillation technique (FOT) in preschool children with a history of wheezing. Methods: FOT respiratory resistance (Rs) and reactance (Xs) were assessed in children at 6, 10, 15, and 20 years of age, as well as resonant frequency (Fres), were measured in kindergartens. Children were labelled to have a history of wheezing (WZ) if, based on questionnaires, they had had a diagnosis of asthma, or >3 episodes of WZ, ever, or WZ during the previous year. All children had no respiratory symptoms or signs at the time of testing. Post-bronchodilator (BD) impedance was assessed 15 min after administration of salmeterol 200 mcg via MDI and a spacer.

Results: A total of 165 healthy (H) children (82 female; median age 4.8 yr, range 2.9-6.1) and 64 WZ children (25 female, median age 4.6 yr, range 2.7-6.0) were evaluated. Mean (SD) Rs, Xs and Fres are reported in the table. Post-BD changes were not significantly different in the two groups.

Conclusions: Rs, Xs and Fres were not significantly different in asymptomatic preschool children of a history of WZ and in controls. Other indices, such as the area under the curve of Xs, need to be investigated.

P1117 Detection of bronchodilator effect by spirometry in preschool asthmatic children

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Study objective: Measuring bronchodilator (BD) response in school children by spirometry is an integral part of asthma diagnosis and assessment. However, the applicability of the spirometry criteria to preschool age is questionable. We measured changes in forced spirometry indices to determine their ability to detect BD-response in asthmatic preschool children.

Patients and methods: Data of 288 children (aged 2.6-6.9y) were analyzed. Spirometry tests were carried out before and 15 minutes after BD-inhalation in 145 asthmatic children. Data was compared to that of 39 controls and to that after inhalations of saline (n=104 asthmatics)administered similarly. An increase above 12% from baseline FEV1 after intervention was considered significant. Response of other spirometry indices were related to change in FEV1.

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P1118

Where there’s smoke there’s fire! What is the function?

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Morbidity and mortality from smoke inhalation occurs in victims of fire. This study’s purpose is to report infant pulmonary function (IPF) in children exposed to smoke from a building fire. The children received care in another facility and were referred to our center for IPF. IPL was performed on 45 children; 23 females, 22 males mean age of 114 weeks; range 50 to 173 weeks at the time of testing. Time to testing after the fire was 8.4 months (range 3-17 mos). Conscious sedation was used for raised Vocal than subglottal compression as the IPL technique. Pre-bronchodilator results were obtained on 45 children.

The low TLC group also had significantly lower FVC and FEV 1 than the normal TLC group. The results of 45 children showed low normal TLC and FVC. When the results compared abnormal TLC% versus normal TLC%, the low TLC% group also had significantly lower FVC and FEV 1 than normal TLC% group. These findings are similar to the decline in FVC found in World Trade Center workers. Mildly increased specific compliance of the respiratory system was also found. No restrictive pattern was detected. Serial IPFT assessments in our cohort is required to validate present data.

References:

P1119

Longitudinal assessment of lung function in children and adolescents with sickle cell anemia

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Aim: Lung function studies in children with sickle cell disease (SCD) have not identified consistent abnormalities. The results, however, of two cross-sectional studies suggest restrictive abnormalities become more prominent with increasing age. Our aim was, by undertaking serial comprehensive assessments in SCD children, to further characterize any changes in lung function with increasing age.

Methods: Two cohorts of SCD children were recruited. Cohort 1: 21 children, mean age at baseline 8.1 (range 2.9-12.0) years and mean length of follow-up 9.0 (8.1-9.8) years. Lung function was assessed by spirometry and body plethysmography.

Results: Lung function declined significantly in both cohorts. The results are expressed as median (IQR) and percentage predicted for height.

Comparison of the data from the two cohorts demonstrates a faster decline in cohort one.

Conclusion: Children and adolescents with SCD suffer deterioration in lung function with increasing age; the speed of decline is greatest in young children.

P1120

Pediatric pulmonary function testing in infants and toddlers with perinatal burden

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Methods of infant pulmonary function testing (IPPT) represent an important diagnostic tool for an assessment of chronic lung disease in infancy (CLDI). We assessed lung function in a cohort of children with a perinatal burden. We tested 74 infants and toddlers (birth weight 1.47±1.1 kg [mean±SD]; body length at birth 30±6.13 cm, with CLDI). Age at testing was 1.36±0.69 (median 1.35) yrs; body weight 9.0±2.2 kg; body length 76.0±9.7 cm. The whole-body plethysmography (to measure FRCp and sReff), tidal breathing analysis (IPPTE%e), baby resistance/compliance (specific Crs) and rapid thoraco-abdominal compression method (VmaxFRC) were performed. MS Baby Body, VIASYS, USA was used. Standard protocols [1] and proper reference values [2] were used.

IPPT equals 115±4.412% pred (P<0.02), sReff reached 134±6.938% pred (P<0.0005). The response of the control group to bronchodilators or to Saline was negligence.

Other indices increased by 23.4±2.1% (n=69%, 70%, and 74% of the group; p<0.001 for all). The response of the control group to bronchodilators or to Saline was negligence.

Conclusion: Infant pulmonary function testing (IPPT) represents an important diagnostic tool for an assessment of chronic lung disease in infancy (CLDI). We assessed lung function in a cohort of children with a perinatal burden. We tested 74 infants and toddlers (birth weight 1.47±1.1 kg [mean±SD]; body length at birth 30±6.13 cm, with CLDI). Age at testing was 1.36±0.69 (median 1.35) yrs; body weight 9.0±2.2 kg; body length 76.0±9.7 cm. The whole-body plethysmography (to measure FRCp and sReff), tidal breathing analysis (IPPTE%e), baby resistance/compliance (specific Crs) and rapid thoraco-abdominal compression method (VmaxFRC) were performed. MS Baby Body, VIASYS, USA was used. Standard protocols [1] and proper reference values [2] were used.

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Comparison of the data from the two cohorts demonstrates a faster decline in cohort one.

Conclusion: Children and adolescents with SCD suffer deterioration in lung function with increasing age; the speed of decline is greatest in young children.

P1121

Validity of volumetric vest respiratory measurements in preterm infants with changes in posture

Sarah Kent1, Catherine Olden1, Heike Rabé2, Paul Seddon1. 1Respiratory Unit, Royal Alexandra Children’s Hospital, Brighton, United Kingdom; 2Trevor Mann Baby Unit, Royal Sussex County Hospital, Brighton, United Kingdom

Respiratory measurements in unsedated infants are problematic: applying a face mask causes arousal and changes respiratory pattern. We have previously validated a volumetric vest system (FloRight) in normal newborn infants. However, other calibrated chest wall measurements (eg Respirate) lose validity if posture or chest shape changes.

In order to assess whether this system remained valid with chest distortion and changes in posture, we measured tidal breathing in 11 preterm infants (median 30 weeks at birth) simultaneously by mask/ultrasonic flowmeter and FloRight, both in supine (S) and randomised right or left lateral position (L). The following tidal breathing parameters were compared over 20 breaths of stable breathing in quiet sleep: tidal volume (Vt), timing of peak tidal expiratory flow (vtpvfe (%) and expiratory inspiratory time ratio (tI/T).

FloRight measurements were closely correlated with mask measurements in both S and L. Vt S=0.99, L=0.99, vtpvfe (%) 0.94 and 0.96, tI/T 0.97 and 0.96. FloRight Vt measurements were slightly but significantly higher than mask, both in S (1±2ml, p<0.02) and L (1±4ml, p<0.001) but vtpvfe (%) and tI/T measurements were not significantly different.

FloRight accurately measures tidal flow timing parameters in small preterm infants both in supine and lateral posture. Tidal volume measurements are highly correlated but slightly overestimated compared to mask; especially in lateral lying: this could be due to the vest not fully conforming to chest distortion.
Aims: To study the usefulness of a supra-maximal stress protocol to confirm the achievement of a maximal oxygen consumption in cardiopulmonary stress tests amongst obese children.

Methods: It is a descriptive transversal study carried out upon obese children from 6 to 14 years old. An ergospirometry is carried out on them with a treadmill with an incremental maximal stress protocol and after 15 minutes of rest the supra-maximal stress protocol is applied with 105% of the intensity previously obtained.

Results: A total of 24 obese children (15 male, 62.5%) were studied, with an average age of 10.98 years old (±2.18) and an average BMI of 27.44 (±3.31).

A plateau was not found for the oxygen consumption in any instance. A total of the supra-maximal test, the VO₂peak was 2.15 l/min (±0.57), RER 1.16 (±0.58), RER 1.05 (±0.11) and HRmax% 91.5 (±3.18).

Conclusions: The execution of a supra-maximal stress test after a period of rest after a normal test is feasible amongst obese children. The classic criteria that define the success of the VO₂max can be inadequate for this group, thus, carrying out a supra-maximal stress test would be useful in order to verify it.

P1123

Prescription of physical exercise for obese children based on cardiopulmonary exercise tests

Laura Fidalgo-Marrón1, Estela Infanzón-Marrón2, Ester Cid-Parrís1, Alfonso Ortigado-Matamala1, Pilar Sevilla-Ramos1, Jose Maria Emeens-Bustos1, Pediatria, Hospital Universitario de Guadalajara, Guadalajara, Spain; 2Medicine Faculty, Universidad Complutense de Madrid, Madrid, Spain

Aims: To study the differences between the theoretical training zones and those obtained using a cardiopulmonary stress test for the prescription of slight-moderate intensity physical exercise amongst obese children. To correlate the exercise intensity in the theoretical zones and those obtained with the degree of perceived effort.

Methods: It is a descriptive transversal study carried out amongst obese children from 6 to 14 years old. An ergospirometry was carried out on a treadmill with an incremental maximal stress protocol according to the ATS/ERS recommendations. The anaerobic threshold (AT) was calculated using the V-slope method, collecting the HR reading at this point and assigning the perceived effort scale value (PCERT) obtained at that moment. The differences between the theoretical HR at AT and the collected one were subsequently studied.

Results: A total of 28 obese children (17male, 61%) were studied, with an average age of 10.90 years old (±2.43) and a BMI of 27.61 kg/m² (±3.46). The average HR at AT was 117.45 bpm (±15.67) which corresponds to 56.29% (±7.56) of the maximal. Theoretically, the threshold would be in an range around 75% of the maximum, which would make up an average difference of 48.96 bpm (±15.29) (p<0.0001) with the actual anaerobic threshold. The perceived effort value was between 1 and 2.

Conclusions: The prescription of physical exercise for obese children with varied controlled intensities must be personally carried out and based on a cardiopulmonary exercise test feasible amongst obese children. The classic criteria that define the success of the VO₂max can be inadequate for this group, thus, carrying out a supra-maximal stress test would be useful in order to verify it.

P1124

Effects of oral breathing and cervical postural alteration in respiratory mechanics and exercise capacity

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Introduction: Although chronic and persistent mouth breathing has been associated with postural alterations, causing decreased muscle strength, reduction of thoracic expansion and pulmonary ventilation with consequences in exercise capacity, the relationship between these alterations have been little studied.

Objective: To evaluate exercise tolerance and respiratory muscle strength in relation to cervical posture and respiratory mode (oral breathing (OB) and nasal breathing (NB)) children.

Method: An analytical cross-sectional study included 8-11 years old children with clinical orthorharyngology diagnosis for OB. We excluded obese children, with asthma, chronic respiratory diseases, neurological and orthopedic disorders and cardiac patients. All participants underwent postural assessment, maximal respiratory pressures (maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)) and six minute walk test (6MWT).

Results: There were 92 children (30 OB and 62 NB). In the OB group, there was no difference between the means of MIP, MEP and 6MWT between the group with posture alteration (severe and moderate) and normal cervical posture. In the RN group, the mean MIP (70.8±19.1 x 54.7±21.7 cmH2O, p=0.003) and MEP (67.7±22.1 x 50.5±19.5 cmH2O, p=0.002) were higher in the group with cervical postural alteration. The presence of OB determined the decrease of MIP, MEP and 6MWT. The presence of moderate cervical posture had positive relationship in MIP and MEP values.

Conclusion: Oral breathing affects negatively the respiratory biomechanics and exercise capacity. The head posture, altered moderately, acts as a compensation mechanism to improved respiratory muscle function.
110. Risk and detection of childhood asthma and allergy

P1127 Late-breaking abstract: Asthma through childhood; do children remit from their disease?
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Rikshospitalet, Oslo, Norway; 2Faculty of Medicine, University of Oslo, Oslo, Norway

Background and aim: Around 50% of children with early wheeze outgrow their disease according to the literature. In a prospective birth cohort running through puberty, we assessed persistence, remission and relapse of asthma.

Methods: Time-course asthma phenotypes (figure below) were constructed from the 2-10-16 yrs investigations in the Oslo “Environment and Childhood Asthma” study, based on the presence/absence of recurrent ≥2 bronchial obstruction (rBO) 0-2 yrs, and asthma from 2-10 and 10-16 yrs defined as ≥2 of: doctor diagnosis/symptoms/asthma-medication use. Positive bronchial hypersensitivity (BHR) at 16 years required a PD20-metacholine <8 μmol.

Results: Of the 550 subjects (52% boys) attending all investigations, 228 children had rBO/Asthma in at least one time-period, 143 with rBO (figure below). Among rBO children at 16 yrs, 34% had asthma, whereas 51% of those in remission had symptoms, medication use and/or BHR, compared to 27% with never asthma (p<0.0001), thus 33% only were without signs of asthma.

Conclusion: Only one third of the early wheezers were in true clinical remission by 16 years. Thus early recurrent “wheeze” appears less benign than commonly reported.

P1128 Late-breaking abstract: Maternal genetic asthma predisposition affects pulmonary microRNA profiles in neonatal offspring
Stefan Dehmel1, Agnieszka Pastula1, Rabea Imker1, Nikola Schulz1, Oliver Eickelberg1, Adalbert Roscher2, Susanne Krauss-Etschmann1,2
1Department of Pediatrics, Oslo University Hospital, Ullevaal, Oslo, Norway; 2Department of Pediatrics, University Hospital, Ulm, Germany; 3Department of Pediatrics, University Hospital, Münster, Germany;

Methods: We asked if maternal genetic asthma predisposition affects pulmonary miRN profiles during an early developmental stage and might therefore influence lung development.

Aim: We asked if maternal genetic asthma predisposition is sufficient to affect pulmonary miRN profiles in offspring that do not bear the genetic asthma risk. To address this question, we used female mice with a heterozygous deficiency for Tbx21 as they develop spontaneous airway remodeling and airway hyperreactivity (Fitto et al., Science, 2002, 299:336).

Methods: Female C57BL/6-Th21+/- mice were mated with WT males. Neonatal lungs from male WT offspring of dams with (Tbx21+/-, n=5) and without genetic asthma predisposition (WT, n=3) were removed within 24h after birth and total mRNA including small RNAs was extracted. Duplicate pools of RNAs were subjected to miRNA expression profiling (ABI, TaqMan® Array microRNA cards). In silico target prediction was performed for miRNAs with a >1.5x change followed by pathway analysis (DEANA-nmapth, TargetScan).

Results: Male WT offspring of Tbx21+/- dams showed an up-regulation of 14 of 750 miRs (1.5-2.1x), while 17 miRs were down-regulated (1.5-4.7x) compared to male WT offspring of dams without genetic asthma predisposition. Pathway analysis showed a significant enrichment of target genes within the WNT pathway (49 of 154 genes). MiRs 27a* and 124 were found to target multiple genes (≥15) in the WNT pathway suggesting a key regulatory function for these miRs in WNT signaling.

Conclusion: These data show that maternal genetic asthma predisposition affects pulmonary miRN profiles during an early developmental stage and might therefore influence lung development.

P1129 Revisiting the September asthma epidemic
Conrad Capili, Robert Jacobson, Xujian Li, Young Juhn. Community Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, United States

Background: September asthma epidemic has been well documented. Whether a similar pattern of asthma exacerbation is observed in children returning to school from winter and spring break is unknown.

Objective: To assess whether the September asthma epidemic occurs in Olmsted County, Minnesota and determine whether similar asthma epidemics occur after winter and spring break.

Methods: The study included all asthmatic children ages 5-18 who had received medical care at our institution as of March 12, 2008 (n=3092). Asthma status was defined by physician diagnosis in the medical records. We compared the frequency of all asthma-related hospitalizations, ED visits, outpatient visits, and corticosteroid therapies for acute asthma symptoms between August and September of 2008 and 2009. Similarly we compared the frequency of all asthma-related visits or treatments between during and after spring break and between during and after winter break.

Results: The frequency of asthma-related visits and treatments in September of 2008 and 2009 was 2.1% per person-month, which was significantly greater than that in August of 2008 and 2009 (1.2% per person-month) (p<0.003). Similarly, the frequency of asthma-related visits and therapies during the period after spring break of 2008 and 2009 (1.1% per person-month) tended to be greater than that during spring break (0.75% per person-month) (p=0.063). There was no difference in asthma-related visits or therapies during and after winter break (p=0.59).

Conclusions: The September asthma epidemic does occur in our study setting, but this may not be a September-specific concern. Clinicians should consider a step-up therapy and reinforce medication compliance for asthma exacerbation-prone children returning to school.

P1130 Asthma symptoms in pediatric patients: Differences throughout the seasons
Ellen Koster, Jan Raaijmakers, Susanne Vijverberg, Anke-Hilse Maitland-van der Zee. Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands

Background: Seasonal variation in asthma has been widely recognized. The aim of this study was to describe seasonal patterns of asthma symptoms and medication use in a cohort of pediatric asthma medication users and to study determinants of seasonal childhood asthma.

Methods: For this study, 602 children participating in the PACMAN (Pharmaco-genetics of Asthma medication in Children: Medication with Anti-inflammatory effects)-cohort were included. Parents were asked about their child’s respiratory symptoms and rescue medication use over the past year.

Results: There was a decline in asthma symptoms and medication use during the summer period and a peak occurred from autumn to spring. The prevalence of wheeze ranged from 3% in summer to 56% in autumn. The prevalence of respiratory symptoms and medication use was significantly lower during summer (p<0.0001). Oral steroid and antibiotic use and strong parental necessity beliefs were associated with uncontrolled asthma, regardless of seasonality. Allergic rhinitis was associated with an increased risk of uncontrolled asthma during spring (RR: 1.3, 95%CI: 1.1-1.6) and summer (RR: 1.2, 95%CI: 1.0-1.4). Eczema was associated with a higher risk of uncontrolled asthma during autumn (RR: 1.2, 95%CI: 1.0-1.4) and winter (RR: 1.2, 95%CI: 1.0-1.4).

Conclusions: We showed seasonal patterns in asthma symptoms and medication use. We showed associations between allergic rhinitis and asthma control during spring/summer and eczema was associated with uncontrolled asthma during au-
tumm/winter. Seasonality in asthma morbidity and health care use is most likely associated with atopic constitution and viral infections, which are common during fall, winter and spring.

P1131 Air pollution and asthma hospitalizations in children
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Introduction: Short-term exposure to air pollution can trigger asthma hospitalizations in children, but it is not known which components of air pollution are most important. There is no available evidence on the particular effect of ultrafine particles (UFPs) on admission for asthma.

Aim: To study whether short-term exposure to increased air pollution levels is associated with hospitalizations for asthma in children.

Hypothesis: 1) The association between asthma admissions and air pollution is stronger with UFPs than PM10, PM2.5, NOx. 2) Infants are more susceptible to the effects of exposure air pollution than older children.

Method: Daily count of hospital admissions for asthma in children aged 0-18 years were extracted from Danish National Patient Registry between 2003 and 2008, from hospitals located within a 15 km radius from the central fixed urban air pollution monitor in Copenhagen. Time-stratified case-crossover design was applied and data analyzed using conditional logistic regression to estimate the effect of air pollution on asthma admissions.

Results: We detected a significant association between asthma hospitalizations in children aged 0-18 years and NOx (ORs ratio: 1.11, 95% CI: 1.05-1.17), PM10 (1.07, 1.03-1.12), and PM2.5 (1.09, 1.04-1.13), and none with UFPs. Infants had higher risk of being hospitalized for asthma than older children, for all pollutants, but were not statistically significantly more susceptible.

Conclusion: A significant association showed between air pollution and hospitalization in children, with infants possibly most susceptible. Gases (NOx and NO2) originating from traffic showed strongest associations, while UFPs showed no effect.

P1132 Comparison of prevalence of childhood asthma in two different African-American communities in Columbus area. A pilot study
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Asthma prevalence is on the rise and children in minority communities have the highest prevalence.

Objective: Pilot study done at Mission Day School (private elementary school) and at New Salem Baptist Church (urban inner city neighborhood) in Columbus, OH, to understand asthma prevalence in two communities with same racial but different socio-economic status. All children were African Americans.

Method: Study was done using validated “Easy Breathing Survey (Hall CB et al. J Pediatr 2001;139:267-72)” with 4 questions. A positive response to any of the 4 questions has 94% sensitivity for asthma and specificity [95%CI] of each question between 66% - 86%.

Results: Questionnaire was sent to 105 families at both places. Fifty four families completed the survey. MF 28:26 and 27:26, family history of asthma 24 and 27, known asthma triggers in 16 and 18 children respectively. Nine (16%) children at both sites had previous diagnosis of asthma and among them, 8 at school and all nine at church still had positive responses to survey. Additional 27 children at school and 26 at church responded positively to questions on survey though none of them had a previous diagnosis of asthma and about one third of them at both sites had required acute care for asthma within a year.

Conclusion: Asthma prevalence is high in African American community irrespective of their socio-economic status. In the majority, symptoms are not well controlled. More than half of children at both sites had positive survey suggesting that they might have undiagnosed asthma.

P1133 Prevalence and risk factors of asthma in urban Canadian aboriginal children
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Background: Clinical experience shows that wheeze is common in children with Down syndrome (DS), but that treatment with anti-asthmatic drugs is usually disappointing.

Aim: To compare the prevalence of current wheeze in children with DS, their siblings, and general population controls.

Methods: This was a case control study in which the International Study of Asthma and Allergy in Childhood questionnaire for respiratory symptoms was completed by parents for 130 children with DS and 167 of their siblings, and for 1/19 age and sex matched control subjects from the general population.

Results: Both wheeze ever and wheeze during the last 12 months was more commonly reported in DS than in their siblings or controls. The relative risk (RR) of current wheeze in DS was 2.8 (95% CI 1.42-5.51) compared to siblings, and 2.75 (95% CI 1.28-5.88) compared to controls. Children with DS were less likely to have received a doctor’s diagnosis of asthma (3.1%) than siblings (4.2%) or controls (6.7%, p<0.04). During 4 yr follow-up, the diagnosis of asthma was confirmed in none of the 24 DS children with current wheeze, and atopy was found in none of them. Chronic rhinitis occurred more frequently in children with DS (40%) than in their siblings (17.3%); eczema did not (14.6 vs 19.2%).

Conclusion: Wheeze is common in children with DS. This is likely to be related to factors specific for DS, and probably unrelated to asthma.

P1134 Nocturnal dry cough in early childhood is a risk for the development of asthma
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Background: Wheeze in young children is an established predictor of the development of asthma later in life. Cough frequently occurs in childhood as well. So far, little is known about the role of nocturnal dry cough (NDC) in the development of asthma.

Objective: The aim of this study was to investigate the association of NDC at ages 1-7 years, in the presence or absence of wheeze, with doctor-diagnosed asthma at 8 years of age.

Methods: Data from the Prevalence and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort were used, which consists of 3963 children born in The Netherlands. Children were followed from birth up to 8 years of age. Presence of NDC without having a cold, wheeze, and a doctor’s diagnosis of asthma ever with symptoms of asthma in the past 12 months (DDA) was reported yearly by the parents.

Results: The prevalence of NDC at age 1 to 7 years varied from 15.0% at age 7, to 23.3% at age 5. NDC without wheeze was significantly associated with DDA at age 8, except for the age of 1 year (range of Odds Ratios (OR) at age 2 to age 7: 1.82 (age 5) to 7.65 (age 7), range of p-values <0.001<0.048). NDC combined with wheeze showed the most strong association with DDA at age 8 (range of OR at age 1 to age 7: 3.96 (age 1) to 35.96 (age 7), all p-values < 0.000). Wheeze without NDC was also strongly associated with DDA at age 8 (range of OR at age 1 to age 7: 2.06 (age 1) to 29.12 (age 7), range of p-values <0.001<0.003).

Conclusion: These results show that NDC in early childhood is an independent risk factor for the development of asthma. The presence of NDC even increases the risk for asthma in children with wheeze.
P1136
Early childhood infections with rotavirus and norovirus are associated with risk of developing asthma
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Background: The role of early infections in asthma aetiology is not fully understood. Most research has focussed on respiratory infections and, although gastroenteritis has been associated with increased asthma risk, gastrointestinal viruses have thus far received little attention.

Aim: To investigate whether infection with gastrointestinal viruses during infancy is associated with the development of childhood asthma and related atopic manifestations.

Methods: In 591 children from the KOALA Birth Cohort Study, IgG seropositivity for rotavirus and norovirus (GGII.4 and GGL.1) was determined at age 1 year. Gastrointestinal symptoms during the first year were assessed by repeated questionnaires. Associations with childhood asthma at 6-7 years and eczema until age 6-7 years, atopic dermatitis at age 2 years and specific IgE at age 2 years and 6-7 years were analysed using multivariable logistic regression and GEE.

Results: Children seropositive for rotavirus at age 1 year had an increased risk for subsequent asthma (adjusted odds ratio 2.36; 95% Confidence Interval 1.00-5.62) and wheeze (1.90; 1.33-2.71), with the highest risk observed in children with rotavirus infection with intestinal symptoms (5.56; 2.78-7.48). Norovirus GGII.4 seropositivity at age 1 year was associated with decreased asthma risk (0.26; 0.08-0.85), and GGL.1 seropositivity was associated with decreased risk of wheeze until age 6-7 years (0.65; 0.42-1.00).

Conclusion: Early life rotavirus and norovirus infections are associated with wheeze and asthma development. Symptomatic rotavirus infection might reveal an underlying general susceptibility to wheeze and asthma or may be causal factor if viremia occurs.

P1137
Maternal asthma phenotypes and children’s allergy status
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Background: Asthma is a complex heterogeneous disease comprising a number of discrete phenotypes. Allergy status in children tends to differ according to asthmatic phenotype of parents, particularly mothers. Mother’s asthmatic phenotype stipulates for differences in structure and time of allergy onset in children.

Purpose: To study the influence of maternal asthma phenotype on children’s allergy status.

Methods: We evaluated the allergy status in children from birth to 7 years of age born from 117 asthmatic mothers with regard to their asthma phenotypes: 88 (75.2%) mothers had early onset asthma phenotype (defined as asthma developing before 16 years of age), 29 (24.8%) – late onset phenotype.

Results: The prevalence of allergic asthma and other allergic forms (allergic rhinitis and atopic dermatitis) in children by 7 years of life differed (p<0.001, binomial test) depending on the onset asthma phenotype of mothers. Children born from mothers with early onset asthma phenotypes will be at higher asthma and others allergic forms risk (OR=3.04 [CI 1.03-9.132]).

Conclusions: Maternal asthma phenotype influences the onset and structure of allergy in children. Understanding of underlying asthma genesis is needed for protective measures and prognosis of the diseases in children.

P1138
Maternal stress during pregnancy and childhood asthma: The KOALA birth cohort study
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Introduction: Asthma is among the most common chronic diseases in children. The development of the immune system into an asthma-like makeup may begin in utero and maternal stress can drive immune responses. Increase in chronic stress during pregnancy can parallel the rising prevalence of asthma.

Aim: To investigate whether maternal perceived stress during pregnancy increases the risk of developing asthma in childhood.

Methods: Within the KOALA Birth Cohort Study, The Netherlands, maternal perceived stress was ascertained by using the 10-item version of Cohen’s Perceived Stress Scale at 14 and 30 weeks of pregnancy. Associations with parental reported wheeze and asthma (n = 1783), total and specific IgE (n = 360) and lung function (standardized FEV1 and FVC; n=417) at age 6-7 years were analyzed using multivariable regression analyses. Asthma was defined as ever doctor-diagnosed asthma with clinical symptoms and/or the use of prophylactic asthma medication in the last 12 months.

Results: Maternal perceived stress was not associated with asthma at age 6-7 years (stress in first trimester: adjusted OR 0.74; CI95% 0.36-1.51; third trimester: 0.82; 0.43-1.59; or both trimesters: 0.90; 0.43-1.87). Maternal stress was also not associated with allergic sensitization (first trimester: 0.50; 0.19-1.30; third trimester: 0.70; 0.28-1.72; or both trimesters: 0.39; 0.12-1.24). No statistically significant associations were found between perceived stress and FEV1 and FVC, nor between the level of stress (low, medium, high tertile) in the first or third trimesters and any outcome.

Conclusions: This study did not find evidence for an effect of maternal stress in pregnancy on asthma development at age 6-7 years.

P1139
Electronic auscultation of the lungs in children with asthma
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Aim: The aim of this study was to determine the quantitative characteristics of sounds by electronic auscultation in children with asthma.

Materials and methods: 112 children with moderate and severe persistent asthma and 41 healthy child, the control group, aged 7-18 years were included in this study. Sound phenomena recorded on the chest with an electret microphone SAFA (Korea) twice: at admission and on the third day of treatment. Data processing was carried out using Audacity 1.3 audio editing and Adobe Audition 1.5.

Results: The asthmatic children respirophonomogram’s curve didn’t show a smooth amplitude decrease in frequencies over 300-1200 Hz, had the persistence of the peaks in the range of more than 1100 Hz, the sawtooth shape of the curve. Sound characteristics do not depend on sex, age, level of physical development of children.

After treatment we noted the decrease of the respirophonomogram’s curve in amplitude at frequencies exceeding 500 Hz, with preservation of low-amplitude peaks in the range of the asthma frequency (1200 Hz). Thus, the air flow becomes less turbulent and severity of bronchial obstruction is reduced. Correlations between the parameters of respiratory sounds and spirometry and peak flow not revealed.

Conclusions: Asthmatic children characteristic respiratory sounds by the electronic auscultation allows to objectively establish the presence of obstruction in children.
Component-resolved allergy diagnostics identify phenotypes in problematic severe childhood asthma

Methods: This cross-sectional study included 56 children with problematic severe asthma, insufficiently controlled despite 80 μg daily inhaled corticosteroids (budesonide or equivalents). IgE antibodies against 131 individual allergen components from inhalant and food sources were analysed using immunosorbent-phase allergen chips. Airway inflammation (FeNO), lung function (FEV1), and bronchial hyperresponsiveness (methacholine challenge) were assessed in all subjects, and Health-Related-Quality-of-Life (HR-QoL) questionnaires and asthma control tests were completed.

Results: IgE antibodies were detected in 80% (n=45) of children tested. Airway inflammation was greater in these children (FeNO mean, 31 ppb vs 16 ppb, p=0.039) and lung function was reduced (FEV1 mean, 79% vs 92%, p=0.05) compared to children without detectable IgE (n=11, 20%). However, HR-QoL and asthma control test scores, and bronchial hyperresponsiveness, did not differ between these groups. Children (30%, n=20) with specific IgE to >3 (median value) mould/indoor components were more sensitized to specific food components (median 5.9 vs 2.2, p=0.026) compared to 45% (n=25) of children with specific IgE to fewer mould/indoor components. Also, children with IgE to >3 mould/indoor components had increased bronchial hyperresponsiveness (methacholine, dose response slope, 101% vs 31%, p=0.027) and lower HR-QoL scores (5.1 versus 5.7, p=0.011).

Conclusions: Polysensitization to indoor and mould allergens based on component-resolved diagnostics identifies a more severe subgroup of childhood asthma.

Iodine subsidy as a factor in prevention of bronchial asthma (BA) in infants

Object: to evaluate the effectiveness of the prevention of the atopic diseases and BA in babies with the use of the iodine drug. Methods: Evaluation of the health state of the babies having got the iodine with maternal milk in the lactation period from 3 to 6 months (n=117) were studied. 118 babies without iodine donation was the control group. Evaluation of the health state according to the anamnesis, examination, laboratory data and hereditary predisposition to allergic diseases was carried. The indices of median iodurea in state according to the anamnesis, examination, laboratory data and hereditary predisposition was estimated. The indices of median iodurea in basic group it was noted evident decrease (χ²=110.90, p=0.0001). Frequent respiratory infections, especially pneumonia, in the first year of life were less common in children with higher risk of iodine deficiency. Excretion of iodine with urine in babies of the iodine subsidy group was 2.9 times more than in control group (0.32; 3.7 < 3.7). The frequency of the acute respiratory infections in comparison with the control group (2.9±0.3; 3.7±0.5) is more significantly (p<0.05).

Conclusions: Iodine drugs can be recommended to breast feeding mothers (2.9 times of the frequency acute respiratory infections in comparison with the control group).

Corticosteroids as a promoter of T cell regulation in vivo in asthma patients.

Background: In asthma, Th1/Th2 ratio was correlated with vitamin D (r= 0.68; P = 0.0001). A positive correlation was found between FVC percent predicted and vitamin D (r = 0.35; P = 0.027). A negative correlation was observed between serum IL-17 and vitamin D (r = - 0.617; P = 0.001). Th1/Th2 ratios of controls were higher (27.2± 24.13%) than those of patients (13.4± 8.55%; P = 0.0001). In asthma, Th1/Th2 ratios were correlated with vitamin D (P = 0.045). The Th1/Th2 ratio was significantly decreased in asthmatic children. A positive correlation was observed between vitamin D and IL-10+ cells (r = 0.428; P = 0.008). A correlation was observed between the percentage of CD25+FoxP3+ Treg cells and vitamin D values in asthmatics (r = 0.368).

Conclusions: Asthma was associated with lower serum Vitamin D levels despite high levels of sun exposure. Our findings suggest that vitamin D is an important promoter of T cell regulation in vivo in asthmatic patients.
developing before 16 years of age) and later-onset asthma and in the group of pop-
ulation control. The genetic polymorphisms –590 C/T were studied by PCR-RFLP
analysis.
Results: The frequency of –590 C allele of the IL-4 gene was significantly higher in
the group of patients with asthma (p = 0.0366) as compared to the population
group. The analysis of distribution of the –590 C/T genotype showed significant
increasing of the frequency of this genotype in the group of patients with later-onset
asthma (p = 0.0231) as compared to the early-onset asthma group of patients.
Conclusions: Asthma is caused by genetic and environmental factors and this
chronic disease is genetically heterogeneous. Our data show that –590 C/T IL-4
polymorphism plays a role in disease formation and could be treated as a prognostic
gene marker of the risk of later-onset asthma.

111. Paediatric respiratory infection: signs, symptoms and sequelae

P1147 Effects of respiratory viral infections on the lower respiratory tract of
children, especially asthmatic children
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Aim: Recent studies strongly suggest that some respiratory viruses are associated
with exacerbation of asthma. We examined their characteristics and their effects
on children with acute lower respiratory symptoms and asthma.

Method: We examined some respiratory viruses in nasopharyngeal swabs using
the polymerase chain reaction (PCR) assay or RT-PCR and analyzed their clinical
data obtained from 107 children (M/F: 70/37, mean age 25.3±2.7 months) with
lower respiratory symptoms who were treated in our hospitals between January and
November 2010. From clinical records, we prospectively investigated the clinical
symptoms of the children.

Results: RSV was detected in 27 samples, HRV in 31, HRV and RSV together in 4,
HRV and HBoV together in 2, EV in 7, PV in 5, HBoV in 2, and Adv in 2, but no
virus was detected in 29. In the RSV group, asthmatic children numbered 10 and
non-asthmatic children, 17, (of whom 11 were inpatients and 6, outpatients).
The mean age of the inpatients (9.3±8.2 months) was significantly less than that of
the outpatients (26.2±14.2 months) (p=0.003). In the HRV group, the frequency of
severe respiratory symptoms was significantly higher in asthmatics than in non-
asthmatics (p=0.04). The mean age of the asthmatic inpatients tends to be
higher than that of the asthmatic outpatients.

Conclusion: Younger children are more susceptible than older children to severe
respiratory symptoms in RSV infections, while, asthmatic school-age children tend
to have severe asthmatic symptoms with HRV infections. These findings suggest
that asthma exacerbation in school-age children may be associated with HRV
respiratory symptoms in RSV infections, while, asthmatic school-age children tend
to have severe asthmatic symptoms with HRV infections.

P1148 CARESS: The Canadian registry of palivizumab (2005-2010)
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Objective: To evaluate the current management of children at high-risk of RSV
infection who received palivizumab prophylaxis in tertiary care centers and com-
munity settings using a Canadian Registry Database.

Methods: A prospective, observational, registry of children who received ≥1
dose of palivizumab during the 2005-2010 RSV seasons across 29 sites. Data on
palivizumab utilization and compliance, and outcomes related to a respira-
tory infection were collected monthly until the full course of palivizumab was
completed.

Results: 7699 infants were enrolled, with an average age of 5.4±4.6 months.
Participants were typically male (56.4%), Caucasians (71.5%), with an average
gestational age (GA) of 32.2 (SD 6.0) completed weeks. 5237 (68.0%) infants
received palivizumab for prevention (435 completed weeks GA) only, 766 (9.9%)
for congenital heart disease, 646 (8.4%) for chronic lung disease and 1050 (13.6%)
for other risk factors (e.g., CNS disorders, airway anomalies and cystic fibrosis).
Participants received an average of 3.9 (SD 1.6) injections, with 30040 doses given
overall. 5.5% of patients withdrew from the study. No direct, drug related serious
adverse events were identified. 460 infants had a total of 541 hospitalizations
for a spectrum of respiratory tract illnesses resulting in a hospitalization rate of
6.0%. The overall RSV positive hospitalization rate was 1.47% with no mortal-
ity. Living with siblings was significantly correlated with a shorter time to first
RSV-positive hospitalization (B=0.615, df=1, p<0.046).

Conclusions: The RSV hospitalization rate observed in the 2005-2010 RSV sea-
sons was similar to that found in several published reports of infants receiving
prophylaxis (range 1.3%-5.3%).

P1149 Increasing immunosuppression despite high load of respiratory viruses:
Fludarabine as rescue treatment in alloreactive lung disease
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Background: Allo immune lung syndromes (alloLS) as Bronchiolitis obliterans
syndrome and idiopathic pulmonary syndrome are life threatening complications
after allogeneic hematopoetic stem cell transplantation (HSCT) or lungtransplan-
tation (LTX; rejection). Respiratory viral infections (HRV; HBoV) may trigger these alloLS. If
conventional treatment with corticosteroids is not effective, 2nd line therapy may
be needed.

Aim: To describe safety and efficacy of the T-cell depleting agent fludarabine to
treat allo immuneLS due to viral infections in the presence of viral infections.

Methods: We describe 5 patients (4 HSCT, 1 LTX) with steroid refractory alloLS
who were therefore treated with fludarabine. 30mg/m2 on a weekly basis. Viral
prevalence of respiratory viruses was monitored by quantitative PCR before and
during treatment.

Results: The five patients all initially had good engraftment, but developed res-
piratory complications. 4 patients were positive in BAL and/or nasopharyngeal
aspirate with cycle threshold (CT values <30 for rhinovirus (2), parainfluenza
and RSV (1) and adenovirus (1)). 4/5 patients had initial response after mean 2.4
(range 1-4) courses. The LTX patient improved clinically as well as for FEV1
for 2 months and then had a relapse with progression of the alloLS. One patient
died from aspergillosis after 2 months. 3 patients had sustained response. Viral
load (expressed in CT values) remained high in all patients, without occurrence of
systemic disease.

Conclusions: Fludarabine is feasible and an effective 2nd line treatment of steroid
refractory allo immune lung syndromes, without an increase in viral load. This
empirical treatment now deserves a controlled study.

P1150 Lung function of preschoolers with parapneumonic effusions complicating
community acquired pneumonia
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Background: Parapneumonic effusions as a complication of community acquired
pneumonia (CAP) in children show an increasing prevalence.

Aim: To monitor expiratory Inspiratory Resistance (Rint), Lung Clearance Index
(LCI) and chest X-Ray among preschoolers with parapneumonic effusions.

Methods: We evaluated children hospitalized with pleural effusion as a compli-
cation of CAP. Expiratory inspiratory resistance (Rint) and Lung Clearance Index
(LCI) were measured on the day of discharge and six months later.

Results: 13 preschoolers, aged 3.5±1.21 years were studied. In 1/13 (84.6%)
Streptococcus Pneumonia was isolated. 84.6% had chest drainage, intratracheal
urokinase was administrated in 69.2% of the children. Two children developed
broncho-pleural fistula and one pericarditis. Lung decortication was documented in
1 child. 38.4% of the patients had abnormal chest X-ray, 6 months later. Children
with pleural effusions had significantly higher Rint on day of discharge (1.12±0.34
pm 0.78±0.20 kPa L-1 second, p<0.001). Six months later Rint was reduced to
normal levels (0.77±0.31 kPa L-1 second, p<0.001). Children with pleural effu-
sion had significantly higher LCI compared to controls (mean difference [95% CI]
2.8 [1.9, 3.8], p<0.001). Six months later, 46.15% of the children had still
significantly high LCI compared to controls [95% CI] 2.2 [1.3, 3.3] p<0.01).

Conclusions: One third of preschoolers with pleural effusions had an abnormal
chest X-Ray, while half of the children had significantly high LCI six months later.
LCI is a sensitive marker that detects abnormal lung function and could be
used to monitor preschoolers with parapneumonic effusions complicating CAP.

P1151 Recurrent respiratory tract infections in the preschoolers and IgG3 deficiency
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Introduction: Recurrent respiratory infections (RRI) are a common cause of
morbidity during childhood.

Materials and methods: We report four cases of otherwise healthy preschool
children who were referred to our paediatric allergy clinic for lower RRI with
wheezing, crackles, cough and rhinitis, mostly during the autumn and winter

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months, since they started attending kindergarten. They were being treated with antibiotics, inhaled beta-2 agonists and corticosteroids for the exacerbations. They were on prophylactic therapy with fluconazole 200g/day and montelukast 4mg/day, with no improvement. There was no history of atopy and the skin prick tests to common allergens were negative. Chest-x-ray and sweat test were normal. All patients underwent an immunologic screening that included CBC, ESR, CRP serum concentration of IgG, IgA, IgM, IgG1, IgG2, total IgG and IgG subclass levels. The major Ig isotypes and the IgG subclasses were quantified by rate nephelometry. The laboratory investigation results were all within normal limits except for IgG values which was in all patients below the 5th centile, based on published Greek normative data. IgG3 levels were: patient 1, aged 3.5: 10.5mg/dl (normal values 17-90), patient 2, aged 4.5: 20.7mg/dl (normal values 24-85), patient 3, aged 5.3: 16-3mg/dl (normal values 24-85), patient 4, aged 6: 14mg/dl (normal values 22-100).

Conclusion: IgG3 deficiency should not be ignored as a possible cause of RRI. Although it may be a transient phenomenon, it is prudent to follow these patients as some might evolve into common variable immunodeficiency. Moreover the use of increased doses of inhaled or systemic corticosteroids may delay the clearance of the virus from the respiratory tract.

P1152
Abdominal pain as a predictor of pneumonia in children
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Introduction: The abdominal pain may occur in children with pneumonia. When it is present, becomes an important symptom because it focuses attention on diagnostic evaluation to cause errors in diagnosis.

Methods: We prospectively studied 258 children aged 3 to 14 years who were admitted to the hospital with a diagnosis of pneumonia.

Results: The dominant initial clinical presentation in 22 (8.5%) of the patients was acute abdomen and the duration of the pain in patients before the diagnosis of pneumonia was established. Respiratory rate on admission >40 was in 14/22 (63.6%) of the patients. Seventy-three percent of the patients had temperature >38°C and 40°C WBC >17,000/mm³ was seen in 15/22 (68.2%). Auscultation abnormalities were present in 17/22 (77.3%) patients. The diagnosis was confirmed in all by chest radiography. It was observed that left-sided pneumonia is capable of mimicking appendicitis almost frequently as right-sided pneumonia. All abdominal symptoms disappeared in all children following the treatment of pneumonia, and no sequelae were observed.

Conclusions: In children presenting with acute abdominal pain, pneumonia must also be evaluated before a surgical procedure should be performed in a child with abdominal pain of unknown cause, especially if there are respiratory symptoms, fever and increased white cell count. Prompt diagnosis is essential, not only to avoid surgical intervention but also to start therapy early and to prevent possible complications of pneumonia.

P1153
Development a set of reagents for real-time PCR diagnostics and surveillance of infections caused by B. pertussis, B. parapertussis and B. bronchiseptica
Maria Praded, Tatiana Selezneva, Svetlana Yatsyshina. Bronhadenitis TB is the most common form of tuberculosis disease in childhood. In Bulgaria about 67% of all patients newly diagnosed children with this diagnosis. The purpose of this study was to determine the diagnostic capabilities of the T SPOT TB in this form of TB disease. In a period of one year were examined in 50 children ages 0-12 years treated in ower hospital with tuberculosis of lung lymph nodes. The diagnosis was set based on history, clinical, microbiological and radiological check you. TST and T SPOT TB test were performed simultaneously in the studied children. It was investigated the relationship between immunological samples TST and T SPOT TB compared contacted hectic age, BCG status and spatum smear microscopy. If no children with TST negative samples, 44% were normergichni reactions to 15 mm. 56% were hyperergic—a 15 mm. In a study with T SPOT TB 28% gave negative results and 72% positive. Most children 44% responded to both applied antigen, 20% of the CFP 10 and only 8% of ESAT 6. As a result of the study made the following conclusions: 1. T SPOT TB has in place in the diagnosis of tuberculosis especially in countries with compulsory BCG vaccination Bulgaria 2. T SPOT TB has a better diagnostic capabilities in major age groups 3. It was a good correlation between the two tests - the percentage of correlation 80%. 4. The sensitivity of the T SPOT TB was 70% and 90% in TST

P1154
Diagnostic capabilities of the T SPOT TB in children with tuberculous bronhadenitis: University Clinic for Lung Diseases – Sofia, Bulgaria
Svetlana Velizarova, University Clinic for Lung Diseases, Medical University, Sofia, Bulgaria

In order to evaluate the clinical manifestations, management and outcome of childhood lung abscesses in Sofia, Bulgaria, a retrospective chart review of 35 pediatric with LA from September 1995 to September 2010 was conducted. Among the 37 patients (20 males and 17 females), 51, 4% (18/37) were primary lung abscess and 49,6% (17/35) had underlying chronic diseases (secondary lung abscess). The predisposing factors of the primary group (n = 18) included 16 cases of respiratory tract infection and 2 with laceration wound. The underlying diseases in the secondary group (n = 17) included 11 cases of hematologic disorder (64,7%), 4 of congenital heart disease, and 2 each of hyperimmunoglobulin E syndrome. 14 patients underwent diagnostic tapping, including echo-guided aspiration (11 cases) and computed tomography-guided percutaneous needle aspiration (2 case). Positive yield rate from aspiration in a secondary group was 50% (7/14). Surgical intervention was performed in 10 of the secondary group and in 1 patient from the primary group. The pathogens were identified in 17 patients (49,6%): 5 with oral flora, 4 with Staphylococcus aureus plus other pathogens, 1 with St. aureus alone, 2 with Pseudomonas aeruginosa plus Proteus mirabilis, 4 with P. aeruginosa alone, and 1 with Aspergillus. The average duration of parenteral antibiotic use was 20 days. 2 cases (5,4%) died due to poor control of the underlying diseases, and 3 of the patients (10,8%) had sequelae (3 with bronchiectasis and 1 with lung fibrosis). Early percutaneous aspiration has an important role in identification of pathogens. Oral anaerobes and S. aureus are the core pathogens in primary lung abscess and gram-negative pathogens should also be considered in secondary LA.

P1155
Connective tissue disorders as the factor that changes clinical course of community-acquired pneumonia in children
Zoia Nestereenko1, Olena Ivanivna2. 1Department of Pediatrics, Faculty of Preclinical Studies, Lugansk State Medical University, Lugansk, Ukraine; 2Outpatient Department, Lugansk Municipal Children’s Hospital No.2, Lugansk, Ukraine

Aim: To study peculiarities of clinical course of community-acquired pneumonia in children.

Methods: 64 children with CAP aged 1-18 were studied during one year. Patients were divided for analysis by age groups (range 2-3 to 9-12 years) and gender. All cases were divided for following: children aged 1-3 (group A, n = 16), and aged 4-8 (group B, n = 48). All patients had manifestations of CTD. CAP was clinically and radiographically diagnosed with detection of serum antibodies (IgG and IgM) against atypical macromolecular pathogens measured by enzyme-linked immunosorbent assay (ELISA).

Results: All patients had CAP caused by atypical pathogens with indistinct clinical manifestations and symptoms. Recurrent course of CAP was in 54 (84,4%) patients. CAP caused by Chlamydia pneumonia (Cp) was more frequent in group A – in 15 (93,7% of the group) patients. CAP caused by Mycoplasma pneumonia (Mpm) was more frequent in group B - in 44 patients (91.6% of the group), in 6,8% - together with respiratory virus. Positive radiography should be performed in a child with abdominal pain of unknown cause, especially if there are respiratory symptoms, fever and increased white cell count. Prompt diagnosis is essential, not only to avoid surgical intervention but also to start therapy early and to prevent possible complications of pneumonia.

P1156
Clinical management and outcome of childhood lung abscess (LA): A 15-year experience
Oleksander Katliv, Dmitro Dmytriiev, Oleksander Marulov. Pulmonology, Vinnitsa National Medical University, Vinnytsia, Ukraine

In a study with T SPOT TB 28% gave negative results and 72% positive. Most children 44% responded to both applied antigen, 20% of the CFP 10 and only 8% of ESAT 6. As a result of the study made the following conclusions: 1. T SPOT TB has in place in the diagnosis of tuberculosis especially in countries with compulsory BCG vaccination Bulgaria 2. T SPOT TB has a better diagnostic capabilities in major age groups 3. It was a good correlation between the two tests - the percentage of correlation 80%. 4. The sensitivity of the T SPOT TB was 70% and 90% in TST

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209s
P1157
Clinical characteristics of pediatric patients affected with H1N1/2009 pandemic influenza A virus who needed hospital admittance in the western region of Guatemala
Kenneth Escobar1, Adolfo Cuá2, Fabiola Moscoso3, Mario Mejía1, 3Pediatrics, Hospital Regional de Occidente, Quetzaltenango, Guatemala; 3School of Medicine, Universidad de San Carlos de Guatemala, Quetzaltenango, Guatemala; 2Central America and Panama Emergent Diseases Surveillance Program, Hospital Regional de Occidente –CDC/CAIP, Quetzaltenango, Guatemala

Introduction: A new variant of the H1N1 influenza A virus caused a pandemic from 2009 until the second semester of 2010.

Aim: To review the clinical characteristics of children who needed admission to our hospital due to a respiratory infection caused by H1N1/2009 influenza A pandemic virus.

Methods: We included in this review all pediatric patients who were admitted to our hospital due to H1N1/2009 influenza A pandemic virus infection, detected by a polymerase chain reaction test in a nasopharyngeal aspirate, sent to the CDC in the US, for accurate viral classification.

Results: We reviewed 40 clinical files. 24 were male; mean age 19 months. 47% were severe malnourished. Three symptoms were predominant in these patients: fever, cough and some degree of respiratory distress. 87.5% of these patients suffered from pneumonia, the main indication to be admitted to the pediatric ward. Hematotic biometries were normal. C reactive protein mean value of 30 mg.d.l in 26 cases. Only one patient received oseltamivir, but 87% (30 patients) were under antibiotics since admission. 10% required mechanical ventilation. An alveolar radiological pattern was seen in 70% of the chest X rays. Mean time hospitalization 7.5 days. The primary outcome of the study, mortality rate, was 7.5% (3 cases).

Conclusions: The mortality due to H1N1 2009 influenza A pandemic virus was low, even though most of our patients were malnourished, had pneumonia and did not receive antiviral treatment. This data correlates with data from other series in which mortality rate from this new pandemic influenza virus was lower than expected.

P1158
Outcome of H1N1 infection in hospitalised paediatric patients in a tertiary hospital
Department of Child Health, Department of Infectious Diseases, Sultan Qaboos University Hospital, Muscat, Oman

Introduction: In Oman, a total of 7040 cases tested positive for H1N1 with 31 deaths, till February 2010. We describe the clinical characteristics of children admitted to Sultan Qaboos University Hospital (SQUH) from September 2009 to February 2010.

Methods: The clinical data of all children with influenza like illness were reviewed. The diagnosis was confirmed in 38 cases by positive RT-PCR assay.

Results: A total of 243 children were admitted with influenza like symptoms, out of which 38 tested positive for H1N1. The mean age group was 4 years 1 month. The time between onset of symptoms and admission ranged from 1-22 days. The duration of admission from 1-22 days. LFT was abnormal in 2 children. None of the confirmed cases had been vaccinated. The number of children treated with peripheral anti-tussives (leodropropizine n=101) was higher than with central anti-tussives (codeine and cloperastine n=60).

Conclusions: The number of children treated with peripheral anti-tussives (leodropropizine n=101) was higher than with central anti-tussives (codeine and cloperastine n=60). Percentage of cough resolution was significantly higher with levodropropizine than with central anti-tussives (47% vs. 28% respectively, p=0.0012) (Fig 2). Percentage of no change or worsening was lower for levodropropizine vs. central drugs (3% vs. 18%, respectively).

P1160
Impact of cough on quality of sleep and effect of anti-tussive treatment in children: An observational study
Alessandro Zanzani1, Granulca De Danieli2, Luigi Lanata2, Rossella Balsamo1, Salvatore Cazzato3, Francesca De Blasio4, 1Respiratory Medicine, University of Bologna, S. Orsola Malpighi Hospital, Bologna, Italy; 2Medical Department, Dompi spa, Milan, Italy; 3Department of Paediatrics, University of Bologna, University of Bologna, S. Orsola Malpighi Hospital, Bologna, Italy; 4Respiratory Medicine and Pulmonary Rehabilitation Section, Clinic Center, Private Hospital, Naples, Italy

Background: Cough is one of the most frequent symptoms in children and is the most common symptom for which children are visited by primary care paediatricians.

Methods: We studied 433 children who required a paediatrician specific consultation for acute cough and analyzed quality of sleep and anti-tussive treatment.

Results: The mean age of the children was 6.1 years (DS 3.6). Cough disturbed sleep in 87.5% of children (Fig 1) and in 71% of parents.

Conclusions: Cough disturbed children and parents sleep. Both peripheral and central anti-tussives were effective in reducing cough intensity, with an advantage for levodropropizine in terms of higher cough resolution and lower unsuccessful treatment.
Primary ciliary aplasia as a cause of recurrent respiratory infections in an infertile young man

Mari Canciani1, Sura Bortotola2, Gioia N. Canciani3, Margherita De Santi1,
1Allergy and Pulmonology Unit, Department of Pneumology, University of Udine, Udine, Italy; 2Department of Pneumology, University of Udine, Udine, Italy; 3Noricch School of Medicine, Health Policy & Practice, University of East Anglia, Norwich, Norfolk, United Kingdom; 4Department of Human Pathology and Oncology, University of Siena, Siena, Italy.

We present a case of primary ciliary aplasia (PCA) a rare form of primary ciliary dyskinesia, characterised by the total absence of cilia in respiratory and sperm cells.

B.A. was born to healthy, first-degree related parents (first cousins). A few hours following birth, the patient developed the first of recurrent upper and lower respiratory tract infections. Cystic fibrosis, major immune deficiencies and allergic sensitization were excluded. Chest CT showed diffuse bronchiectasis of both middle lobes. Nasal and bronchial mucosa samples on transmission electron microscopy revealed total lack of cilia and basal bodies on columnar epithelial cells, despite displaying the morphological features of ciliated cells. At puberty, testicular volume and serum hormone levels were normal. Seminal fluid analysis revealed: ejaculate volume of 0.6 ml; pH 8; low sperm concentration (0.5-0.7 million of spermatozoa/ml); and asthenospermia-terathospermia (immotile spermatozoa and ejaculate volume of 0.6 ml; pH 8; low sperm concentration (0.5-0.7 million of spermatozoa/ml); and asthenospermia-terathospermia (immotile spermatozoa and motility). The clinical presentation at birth and the parents’ consanguinity make it unlikely that these changes are the result of infection or exposure to pollutants, thus supporting the hypothesis that PCA can be an inherited disorder.

A neonate with respiratory distress and unilateral pulmonary hyperinflation

Abdullah Yousef1,7, Ella Sugo2,6, Bruce Currie3,6, Pamela Palasanthiran4,6, Adam Jaffe5,6.

Introduction: Bronchial atresia is characterized by a mucus-filled bronchocoele in which fluid is trapped, distorting the normal bronchial architecture.

Case report: A 9-day old boy presented with history of increased work of breathing and cyanosis. Antenatal ultrasound at 22 weeks of gestation demonstrated marked pleural effusion and a right middle lobe bronchial atresia occurring with cCMV infection which may give further insight into the pathogenesis of this rare condition.

A girl with extensive dissemination of thoracic echinococcosis

Iris Grothus1, C.P. van de Ven1, A.W.P.M. Maal2, G. Palles3, J.C. de Jongste4.

A 10 year old girl from Iran was routinely screened for tuberculosis after immigration. She reported chronic cough and chest pain during the past year. A cystic lesion was detected on chest X-ray, and confirmed by a chest CT which also showed no suspicion of chronic lung disease, tuberculosis was excluded and Echinococcus serology was negative. Bronchoscopy showed no abnormalities, BAL cultures were negative and galactomannan was normal. Abdominal ultrasound excluded cystic lesions in the liver. She was treated with antibiotics and her symptoms disappeared. Surgery was scheduled to make a final diagnosis and because of the infection risk, with a diagnosis of infected CCAM and pleural adhesions. Before surgery we made an MRI scan which revealed a massive amount of cilia, occupying a large part of her left hemithorax. We now suspected dissiminated thoracic echinococcosis, and repeated serology, which was now positive. After alendroalcon prophylaxis and treatment of the cyst in the liver, the cystic lesion was resected. The excised tissue was histologically examined. We diagnosed the patient with a new form of thoracic echinococcosis, which might have been prevented by careful medical history taking, which could have detected cyst rupture.

Chronic nonspecific diseases of lungs (CNDL) and iodine deficiency diseases in children

Turidik Bobomuratov, Gulchehra Isakova, Dilshoda Akramova, Almardon Kuziev, Nurbakhaiz Habibullin, Almardon Kuziev.

During the chronic bronchopulmonary pathology as CNDL on children on background of iodine deficiency diseases, accompanied with the chain of unfavorable factors in immune system, metabolic processes which aggravate the clinical course, as well as make it ill effects.

Local cytokine production peculiarities in nasopharyngeal (adenoid) tissue of children with chronic lymph proliferative syndrome of different etiology

Elena Varyushina1, Marina Drudova2, Elena Tyrnova3, Andrey Simbirtsev1.

For estimation of iodine insufficiency degree we defined the concentration of the iodine in single portion of the urine by photometrical method. On 25% examined, median concentration of the iodine in urine was found the moderate iodine insufficiency degree (20-49 Mgl), on 55.8% light degree (50-99 Mgl), but on 19% iodine concentration in urine was above 100 Mgl. Thus, presence of iodine deficiency diseases in children with CNDL, has a definite significance during and outcome of chronic bronchopulmonary process, which requires additional and regular introduction of iodine-containing preparation and thyroid hormone.

Local cytokine production peculiarities in nasopharyngeal (adenoid) tissue of children with chronic lymph proliferative syndrome of different etiology

Elena Varyushina1, Marina Drudova2, Elena Tyrnova3, Andrey Simbirtsev1.

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Proinflammatory cytokines can regulate local inflammatory and immune responses.
during infections of respiratory tract. Production of IL-1α, IL-1β, IL-6 and IL-8 was investigated in children with chronic lymph proliferative syndrome. Biopsies of adenoid tissue were taken in 42 children 3-8 years old during adenectomy or adenotonsillectomy. Cytokine production was detected in cryostat sections using non-direct immunohistochemistry. Neutrophils were stained histochemically. Cytokine-producing cells (mainly macrophages) were counted in sections, results were expressed in units (0 no reaction – 3 high intensity) and percent of positive cases was calculated. I group of children (n=16) had Epstein-Barr virus (EBV), cytomegalovirus (CMV)-infection (past-infection, PCR+DNA VEB, CMV), II group (n=15) – streptococcal infection (ASL=0–200mg/ml), III group (n=11) – unclear etiology. We detected IL-1α, IL-6 in 25-75%, IL-1β in 25%, IL-8 in 75% patients from I group, but at 94.100% cases in II or III groups. Intensity of all cytokines production was the highest in II group (IL-1α 4.00±0.40, IL-1β 1.40±0.35, IL-6 1.53±0.28, IL-8 1.73±0.32 units) and decreased in group I (IL-1α 0.25±0.23, IL-1β 0.25±0.23, IL-6 0.50±0.27, IL-8 0.93±0.36; p<0.05 vs II vs III (beside IL-8), IV vs III. The number of neutrophils infiltrated adenoid tissue showed local inflammation and did not differ significantly among three groups. We conclude that in children with VEB, CMV infection cytokine production is suppressed in comparison with groups with Streptococcal infection or unclear etiology.

112. Paediatric atrophic rhinitis: bronchiolitis, pneumonia, asthma and spirometry in non-respiratory conditions

P1166
Geographical variation in the risk of childhood pneumonia and relationships to socio-economic and health deprivation
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Introduction: Socio-economic deprivation is a recognised risk factor for childhood pneumonia, while the relevance of health deprivation is unknown. The aim of this study was to establish whether there is significant spatial variation in risk of childhood pneumonia and whether this risk was determined by health and socio-economic deprivation.

Methods: Data on childhood hospital admissions in NE England from May 1997-April 2007 (n = 93,252) with a diagnosis of bacterial or lobar pneumonia were extracted from the Hospital Episode Statistics database. The spatial unit was a postcode district, which was linked with data from the health and socio-economic domains of the UK Child Wellbeing Index. Bayesian convolution models were used to model the association between standardised relative risk of admission to hospital with pneumonia in postcode districts and the deprivation indicators.

Results: There were 3874 admissions. From a total of 116 districts, 53 had a significantly different relative risk (RR) using a 95% Bayesian confidence interval (BCI) than that predicted by population alone (31 lower risk, 22 higher risk). The lowest RR was 0.32 and the highest 2.34. When the deprivation indices were included, the median effect of health deprivation was 0.43 (95% BCI 0.27-0.58). The model using only health deprivation provided the best explanation for the data (Deviance Information Criterion for null model 749.68 vs. 744.08 for health deprivation model).

Conclusion: There is substantial variation in the relative risk of pneumonia in different areas of NE England. Health deprivation better explains the spatial variation in risk than socio-economic deprivation.

P1167
Risk factors for recurrent wheezing following bronchiolitis: 3 yrs of follow-up
Giulia Cangiano1, Alessandra Pierangel2, Carolina Scagnolari2, Enea Bonci1, Corrado Molinari1, Paola Pagetti1, Jole Rabbal1, Marianna Ferrara1, Stefano Luciani1, Fabio Midulla1, 1Paediatrics, Sapienza University, Rome, Italy; 2Molecular Medicine, Sapienza University, Rome, Italy

We have previously demonstrated the association between bronchiolitis from Rhino virus (RV) and recurrent wheezing after one year of follow-up (Eur Respir J 2010; 36 (54) P2707). Our objective was to identify wheezing recurrence and related risk factors in infants with bronchiolitis from Respiratory Syncytial Virus (RSV), RV, Bovacivirus (hBoV), Influenza A and B, Parainfluenza 1-3, Metapneumovirus, Adenovirus and Coronavirus detected from nasals washes with RT-PCR. 208 infants (mean age ± SD 2.4±2.1, range 0.07-11.89 months, 89 males) hospitalized with bronchiolitis were evaluated for recurrent wheezing (RW) during 3 yrs of follow-up. Demographic and clinical data were obtained from parents with a structured questionnaire and patient’s medical files. Of the 208 infants, 152 (73%) answered to the phone call. 104 viruses were identified from 92 infants: RSV in 68 (33.9%), RV in 18 (16.3%), hBoV in 17 (18.5%), RSV+hBoV in 10 (10.9%), other viruses in 4 (4.3%). 34.9% of the infants with bronchiolitis had RW at the 3rd yr of follow-up. The related risk factors for RW were blood eosinophil counts > 400 cells/mm3 (OR 9.35; CI 0.95 1.98; 79.0), breastfeeding more than 2 months (OR 2.43; CI 1.20, 4.89) and bronchiolitis from RV (OR 3.17; CI 1.03, 9.79). At the 3rd yr of follow-up, 66.7% of the infants with bronchiolitis from RV have RW comparing to 75.1% of the infants with bronchiolitis from RSV, 30% of the infants with bronchiolitis from RSV+hBoV and 25% of the infants with bronchiolitis from other viruses. In conclusion infants with RW at the 3rd yr of follow-up after acute bronchiolitis seem to be those with atopic predisposition and a specific viral infection.

P1168
Making a bronchiolitis pathway work: If at first you don’t succeed ... Leo Thanikkel, Georgia Spentzou, Roona Amiapratong, Rob Ross Russell. Department of Paediatrics. Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Introduction: Last year we presented a poster asking why we were so poor at following bronchiolitis guidelines. A number of measures were introduced following last year’s poor performance. This year we re-audited the pathway.

Methods: In 2008 we developed a care pathway for bronchiolitis trying to reduce unnecessary investigations and treatments, and optimise support with triage. Over the first winter we failed to produce any impact [1]. Analysis showed that the problem lay in the first hours of admission, and with doctors unfamiliar with the pathway. Formal and informal feedback, and focused teaching was instituted. Monthly data on key targets were collated and disseminated to staff.

Results: Over the first 4 months of the 2010/11 season the use of unnecessary investigations and treatments fell considerably (see table). Median length of stay also fell, from 3 days to 2.0 days.

This translates to significant savings. The reduced length of stay saved 77.4 beddays (~£40,000 (£ 48,000), 0.63 beds) and approximately £1500 (£ 1800) in investigation costs over the 4 month period. There have also been considerable savings in treatment costs.

Conclusion: Our work shows that the introduction of a guideline has to be continuously followed up with clear aims, focused teaching, and careful analysis. We believe that engaging doctors at all levels and regular feedback about progress are essential. Perseverance is important in order for the pathway to pay off; especially in a system where at regular intervals doctors rotate into the department.


P1169
Respiratory syncytial virus (RSV) prophylaxis in special populations
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Objective: To compare palivizumab utilization and compliance, and respiratory infection (RI) outcomes in subgroups of infants at high risk for RSV within the Canadian Registry Database.

Methods: A prospective, observational, registry of infants at 29 sites who received ≥1 dose of palivizumab during the 2006-2010 RSV seasons. Utilization and RI outcomes were collected monthly over the full course of palivizumab Infants <35 completed weeks gestational age without medical conditions who met standard approval criteria (Group 1) were compared to those at high risk of RI due to underlying medical illnesses (Group 2).

Results: There were more infants in Group 1 (n=4880, 84%) than Group 2 (n=9952, 16%). Group 2 included Down syndrome (20.2%), upper airway anomalies (18.5%), pulmonary disorders (13.3%), cystic fibrosis (12.5%), neuromuscular impairment (8.2%), multiple system disorders (6.1%), cardiac disorders (2.7%), immunocompromise (1.8%), and miscellaneous disorders (10.8%). From 2006-2010, the proportion of Group 2 infants increased 4-fold from 5.6% (691/2243) to 19.1% (662/4213). Group 2 was older at enrollment (10.2±9.2 vs 5.3±5.3 months, p<0.005), had more advanced gestational age (35.9±6.0 vs. 30.9±5.4 weeks, p<0.005) and had higher RI (9.0% vs. 4.2%, p<0.0005) and RSV hospitalization (2.3% vs 1.32%, p=0.003) rates. Group 2 infants tended to be less compliant with treatment (69.4% vs 72.8%, p=0.048). Group (p=0.015) was an independent

P1170
Rates of Rx and Ix 2008/09/10 data (%) 2010/11 data (%)

X rays 37.6 16.7
Blood tests 36.1 15.8
Blood cultures 27.0 7.8
Antibiotics 22.3 8.6
Steroids 9.0 3.7

SUNDAY, SEPTEMBER 25TH 2011

Furniture SpA. Visit Chiesi Farmaceutici SpA. at Stand D.30
Birth by caesarean section is associated with asthma and atopic allergies (OR 1.27, 95%CI 0.69-2.36) non-significant association was observed in children without a family history of atopy (p for effect modification=0.06) but not asthma. More specifically, having wheeze (OR 1.36, 95%CI 1.07-1.71) asthma diagnosis (OR 1.41, 95%CI 1.09-1.83) and atopic sensitization (OR 1.67, 95%CI 1.08-2.60). There was some evidence that family history of allergies may modify the effect of caesarean section delivery on atopy (p for effect modification=0.06) but not asthma. More specifically, children with a family history of allergies had double the odds of atopic sensitization if born by caesarean section (OR 2.34, 95%CI 1.20-4.54) whilst a non-significant association was observed in children without a family history of allergies (OR 1.27, 95%CI 0.69-2.36).

Conclusion: Birth by caesarean section is associated with asthma and atopic sensitization in childhood. The association of caesarean delivery and atopy but not asthma is more pronounced in children with family history of allergies.

Physical activity and asthma symptoms in a population-based cohort

Conclusions: Physical activity levels were comparable between children with and without asthma related symptoms, with small differences only seen mainly in children who cough at night. Further analysis will investigate whether this is due to insufficient asthma treatment, and determine potential long-term effects of physical activity on prognosis of symptoms and lung function.

Prevalence of asthma and allergies in the Greek (G/C) and Turkish (T/C) communities in Cyprus

The prevalence of wheezing among 8-8 year-olds was 8.7% vs 11.4% (OR=0.74, p<0.01). Family history of atopy and early nursery attendance were elevated amongst the G/C. Other favourable factors as projected in the hygiene hypothesis were more frequent in the T/C community, including higher proportion in less urban areas (60% vs 34%), bedroom sharing (52% vs 37%) and exposure to farm animals (4.7% vs 6.0%). The same picture emerged in the 13-14 year old group. Controlling for participants' characteristics did not overturn the observed pattern in terms of community in either age-group e.g. the adjusted OR for wheezing remained at 0.73 (p=0.03) in the younger age-group.

Conclusions: Observed differences in the prevalence of risk factors between the two communities did not account for the lower prevalence of asthma and allergies among G/C children, suggesting that other factors not related to the hygiene hypothesis might be at play.

Assessment of primary care doctor’s diagnosed bronchial asthma in schoolchildren

We aimed to assess, whether physical activity differs between children with and without asthma symptoms.

Methods: In a population-based cohort, we collected information on physical activity and respiratory symptoms (wheeze, cough without colds, night cough) by questionnaire at ages 4-8 (N=5212) and 6-10 years (N=4236). We compared prevalence of symptoms between inactive (0-1 hour/day of outdoor play) and active (>2 hours/day) children.

Results: At age 4-8, 4447 children (85%) were active, at age 6-10, 3686 (87%). In 4-8 years olds, 17% of active and 19% of inactive children had current wheeze (OR 1.39, 95%CI 1.04-1.87). 38% vs. 41% had cough without colds (p<0.01, OR 0.77 vs. 0.59) and atopic sensitization (OR 1.67, 95%CI 1.08-2.60). There was some evidence that family history of asthma the diagnosis was confirmed in 82 (44.8%) and 200 (41.5%), respectively.

Study Design: at the time of referral, 166 ((34.5%) were not. In the groups of suspected and established primary care doctor’s diagnosis of bronchial asthma the diagnosis was included in the survey. At referral and during a 6 months evaluation period patient characteristics, history, symptoms, signs and results of type 1 allergy tests, spirometry, post bronchial beta-2 agonist dilation tests, 4-weeks daily measurement of peak flow rates, corticosteroid reversibility trials and exercise challenge tests were entered into a pre-defined electronic form. The secondary centre diagnosis of asthma was based on these data.

Results: 665 consecutively referred children aged 5-18 (mean 8.1 years, 233 girls (35%) and 432 boys (65%), were included in the study. 183 (27.5%) children had a referral diagnosis of suspected asthma, 482 (72.5%) an established referral diagnosis of asthma. In the latter group 316 children (65.5%) were on inhaled steroids at the time of referral, 166 (34.5%) were not. In the groups of suspected and established asthma the diagnosis was confirmed in 82 (44.8%) and 200 (41.5%), respectively.

Conclusions: In more than half of schoolchildren with a suspected or established primary care doctor’s diagnosis of asthma referred to a secondary paediatric re-
ferral centre the diagnosis may not be confirmed. Sensitivity and specificity of the
diagnosis of asthma in schoolchildren established in primary care settings need
further improvement.

P1175
Evidence that children can assess their asthma medication devices
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University Department of Pediatrics, Agia Sophia Childrens Hospital, Athens,
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Introduction: The value of obtaining children’s reports about their health from
questionnaires is important in clinical paediatrics and child health research. FSI-10
questionnaire for asthma devices’ assessment has been developed and implemented
for adult patients. The reliable Greek version has also been used in adults for both
clinical practice and research.
Objectives: The aim of this pilot study was to examine the suitability of Greek
FSI-10 in asthmatic children in order to measure their satisfaction and the usability
of inhalers in daily practice.
Methods: This 8-week pilot study was designed and conducted as an open label,
single-centre, non interventional, notified to regulatory authorities. Patients have
consented in study participation by their legally authorised persons. 33 (15 female)
asthmatic school children aged between 6 and 16 years were on the same device
use at least two months before study enrollment. Four different breath activated
dry powder inhalers (AeroDuo17, Elipenhaler2, Diskin8, Turbahalder17) were used
by study subjects. Questionnaire’s items were child-reported and completed by the
two pediatricians who interviewed in details the selected patients at the end of the
study. All necessary clarifications and explanations were also given by the
physicians during interview.
Results: Evidence that school children can reliably assess their inhalers by us-
ing the Greek FSI-10 was concluded. The questionnaire was easily understood.
Reliability was very good as shown by Cronbach test (Cronbach’s α = 0.925).
Conclusions: Greek FSI-10 may be used in pediatric school aged population.
Minor modifications may improve its measuring properties and reliability. Further
work on this topic is needed.

P1176
Validation of history on atopy and childhood illness in a clinical birth cohort study
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Hospital Gentofte, Health Sciences, University of Copenhagen, Gentofte,
Denmark
Background: The longitudinal birth cohort study is the preferred design for studies
of childhood health, particularly asthma and other atopic diseases. Still, prospec-
tive data collection depends on recollection of the medical history representing
a potential recall-bias.
Aims: We aimed to ascertain completeness of data on atopic disease and other
health symptoms reported in a closely monitored birth cohort study. Possible bias
from questionnaire severity and socioeconomic factors was sought.
Methods: The Copenhagen study on Asthma in Childhood (COPASC) is a clinical
birth cohort study of 411 children. Child health is monitored at 6-monthly clinic
visits from birth till age 3 with a particular emphasis on asthma and other atopic
diseases. Cohort information of 260 children was compared with the records from
family practitioners as an external reference.
Results: A total of 6134 medical events were reported at the COPASC interviews.
Additional 586 medical events were recorded by family practitioners, but not
reported at the interview. None of these missed events were related to atopic
disease. Respiratory, infectious and skin related symptoms showed completeness
above 90%, other diseases showed lower completeness around 77%. There was
no meaningful influence from concurrent asthma or socioeconomic, including
household income, mother’s education or employment.
Conclusion: The COPASC study exhibited full completeness to the main study
objectives, atopic disease, and high completeness to respiratory, infectious and skin
related illness. Our findings support the validity of clinical interviews of parents
in longitudinal cohort studies investigating childhood illness and atopic disease in
childhood.

P1177
Psychogenic cough: Clinical and laboratory characteristics
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Background: A bizarre loud and hoking cough which increases with increased
attention and is absent at night in an otherwise well child suggests a psychogenic
origin.
Aim – method: Clinical and laboratory characteristics of children with psy-
chogenic cough were analyzed retrospectively. Children were followed up in a
Paediatric Respiratory clinic, over a nine year period.
Results: 114 children with psychogenic cough (46% boys) aged 4.5 - 18 years
were evaluated. Mean duration of the cough was 8.6±11.1 months. Clinical
characteristics of cough were: harsh and explosive (85%), coughing and barking
(14%), exacerbating in the presence of medical staff (62%), disappearing with
sleep (98%), not exacerbated with exercise (82%), not accompanied with wheeze
(98%). Fifty-three children (46%) appeared to be under psychological stress, in-
cluding school phobias, attention seeking, or anxiety (28%) and parental strife
(18%). Sixty-three children (55%) had been prescribed antitussive medication,
salbutamol, inhaled and oral steroids, or anti-histamines, with no response. Physi-
cal examination and lung function tests were normal. Among 21% of the children
flexible bronchoscopy was normal. Explanation and discussion of the problems
that appeared to be associated with the cough were beneficial for 81% of the
patients. 6% of cases with persistent symptoms despite reassurance were referred
for psychiatric consultation.
Conclusions: In children with chronic cough, the characteristics of the cough may
be suggestive of psychogenic cough. The physician’s awareness of the possibility
of psychogenic factors in the aetiology of persistent cough may help in early
diagnosis and thus unnecessary and expensive investigations may be avoided.

P1178
Tourette's syndrome manifest as chronic cough in children
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Hospital, Taichung, Taiwan
Background: Tourette’s syndrome (TS) is a neuropsychiatric disorder charac-
terized by the presence of involuntary motor and phonics tics. Some of the involun-
tary phonic tics may present as coughing, grunting, and wheezing. These symptoms
may easily be confused with the symptoms associated with the disorders causing
chronic persistent cough. The purpose of this study was to present our experience
of the clinical manifestation and treatment outcome of the TS.
Material and methods: Retrospective review studies were done from Jan 2008 to
Dec. 2010. There were 8 patients who initially present as chronic cough (cough > 4 weeks) in OPD.
Results: Their ages ranged between 6 and 17 years old. Of these patients, 6 (75%)
were boys, 2 (25%) were girls. The onset of motor tics. All cases showed simultaneously multiple tics. The
most common tics in TS were throat clearing (58%), facial grimacing (48%),mouth
opening (48%), barking cough (38%), head turning (28%), shoulder jerk (28). Two
patients were associated with the behavioral disorders, obsessive-compulsive
disorder (1/8), attention-deficit disorder (2/8). No known of positive familial his-
tory in our patients. All patients suffered from rhinitis more or less and 5/8 could fully remit after aggressive nasal
management except 3 cases.
Conclusion: We would like to point out that TS should also be considered in
children with chronic cough. This may help prevent the potential unwanted effects
of the drugs which are presumptively given to these patients.

P1179
Prognostic importance of congenital stridor occurred during the 1st year of life
in children of five years of age
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Mediko-Somatological University, Moscow, Russian Federation
Introduction: Stridor usually manifests after birth or at the age of 1 month
and most commonly is a symptom of upper respiratory tract infections. But
stridor appears at 2-3 years of age may be suggestive of psychogenic cough. The physician’s awareness of the possibility
of psychogenic factors in the aetiology of persistent cough may help in early
diagnosis and thus unnecessary and expensive investigations may be avoided.
Objective: To evaluate the impact of congenital stridor in infants as a predictor of
chronic diseases.
Methods: We examined 114 1-year old patients with congenital stridor. 60 chil-
dren were included in 5-year catamnesis data. Our cohort consisted of children
with persistent congenital stridor, excluding children with stridor due to ARD or
tracheal intubation.
Results: On their admission to the hospital all children had stridor of various
degrees, 21,9% had regurgitation, 7% - choking, 7,9% - projectile vomiting, 5,3% were
short-winded, 4,4% had sleep apnea and voice change. All children underwent
thorough examination, rhinolaryngoscopy was performed in 94 patients. Laryngomalacia was diagnosed in 80%, accompanied by pharyngolaryngeal reflux
and gastroesophageal reflux in 93.3%. Reflux-spasmodic without inflammatory
changes was found in 53,3%. All patients had connective tissue dysplasia. Mitral
valve failure was present in 35%, PFO - in 16.7%, heart rate abnormalities - in
21,7%. Chest deformations were found in 45%, hypermobility of joints - in 38.8%.
Conclusions: Congenital stridor may serve as a predictor of chronic disorders of
gastrointestinal tract, ENT-system, dysplasia of connective tissue, cardiovascular
diseases. Children with congenital stridor need to undergo detailed examina-
tions and long-term regular medical check-ups in order to minimize the risk of
complications.
P1180
Factors associated and attack rate in adenovirus infection among children with chronic respiratory disease
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Background: In-hospital adenovirus infections spread easily causing a profound impact in morbidity and mortality associated with outbreaks.

Objectives: To identify the attack rate of adenovirus infection in a hospital for children with chronic respiratory diseases (CRDs) and to assess the factors associated to the infection.

Material and methods: Fifty children with CRD were evaluated between June 2010 and October 2010 at Josefina Martinez Hospital. They were exposed during the Winter Campaign to patients with respiratory infections admitted during that period. Case was defined as “Case”. Univariate and multivariate logistic regression models were used to calculate odds ratios and 95% confidence intervals for selected variables: gender, age, tracheostomy and gastrostomy.

Results: Twenty four of chronic patients (48%) were younger than 2 years old and nineteen of them (38%) were 2 to 5 years old. 68% of all children have tracheostomy and 50% of them have gastrostomy. The attack rate was 50% in three months. There was no mortality. Risk factor associated with adenovirus infection was age 0 to 23 months old (OR = 11.1, 95% CI 1.12 - 109.6, p = 0.039). There was no association with other variables.

Conclusions: It is important to strengthen prevention measures for adenovirus infection, and these should be kept as long as viral shedding is prolonged. Closed hospitals allow a rapid dissemination. Infants are highly vulnerable. Tracheostomy is not associated with increased risk of infection.

P1183
Pulmonary function abnormalities in Egyptian sickle cell disease patients
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Background: Pulmonary complications account for significant morbidity and mortality in sickle cell disease (SCD) patients. Abnormal pulmonary functions (PFTs) in these patients include airway obstruction, restriction, abnormal diffusing capacity, and hypoxemia. This study was carried out to assess PFTs among SCD patients, and the effects of different clinical and laboratory variables on PFTs.

Methods: Forty five steady state SCD patients, previously diagnosed and followed up at the Hematology Outpatient Clinic of New Children Hospital, Cairo University, were included. They were homozygous for HbSS and 18 sickle β-thalassemia. Their mean age was 15.1 years with a range of 5-33 years. Clinical, laboratory and PFTs were performed.

Results: Abnormalities of PFTs were found in 57.8% of our patients (n=26, 23 having restrictive and 3 obstructive patterns). According to severity of affection, 44.4%, 8.9% and 4.4% had mild, moderate and severe abnormalities respectively. Patients’ age was the only clinical variable that showed a statistically significant difference between SCD patients with normal and abnormal PFTs (p=0.02) and between those with normal and restrictive patterns (p =0.05). Frequency of vaso-occlusive crisis and serum ferritin level showed a statistically significant relation with severity of pulmonary affection (p=0.01 and 0.01 respectively). No statistically significant difference in parameters of PFTs of patients on hydroxyurea (HU) and those not. Conclusion: Pulmonary function abnormalities, mostly mild and restrictive, were found among our SCD patients. These changes may be more prominent with increasing age. Severity of pulmonary affection was related to frequency of VOC.

P1182
Pulmonary function in children with inflammatory bowel disease do not differ from healthy population
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Crohn’s disease (CD) and ulcerative colitis (UC) are multisystem disorders. Besides inflammatory process in the mucosa of the gastrointestinal tract there is an increasing age. Severity of pulmonary affection was related to frequency of VOC.

Material and methods: Fifty patients with IBD (25 with CU and 25 with CD, mean age 14,19±3,2) and 39 healthy control subjects (mean age 13,97±3,47) were included in the study. All patients from study and control group underwent standard spirometry, whole body plethysmography, assessment of diffusion lung capacity for carbon monoxide (DLCO).

Results: There were no significant differences between study and control groups Lung volumes remain within normal limits. DLCO was abnormal in 9 (18%) and 6 (15.3%) children from study and control group, respectively. We found one (2%) with decreased vital capacity (restriction not confirmed by whole body plethysmography) and two (4%) with obstructive changes in IBD group. In two patients from control group (5.1%) airway obstruction was diagnosed. Small airways tests were abnormal in 13 (26%) subjects from study group and in 13 (33%) control patients.

Conclusion: Pulmonary function in children with inflammatory bowel disease do not differ from healthy population.

P1184
Peripheral airway function in adults with sickle cell disease
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Aim: Impulse oscillometry (IOS) requires minimal patient co-operation and assesses peripheral airway function. Our aim was to determine whether IOS indices were useful to identify lung function abnormalities in adults with sickle cell disease (SCD).

Methods: IOS measurements were performed on 36 adults, homozygous for sickle cell haemoglobin (HbSS), mean age 40.77±13.80 (± SD 13.80) years; the controls were 10 ethnically matched subjects. Respiratory system resistance (Rs) at oscillation frequencies of 3Hz (Rs3), 5Hz (Rs5), 10Hz (Rs10), 15Hz (Rs15) and 20Hz (Rs20), respiratory system reactance (Xrs) at an oscillation frequency of 5Hz (Xrs5), resonant frequency (fres) and reactance area (AX) were recorded. Frequency dependence of resistance between 3 and 20Hz (f-d) was also calculated.

Results: Rs was raised at all oscillometry frequencies in the SCD patients. Xrs5 and AX were increased in SCD patients (p=0.00091, p=0.0006 respectively). The slopes of the linear transformations of frequency dependence of resistance (f-d) curves were negative in SCD patients, but not in the controls (p<0.0001).

Conclusion: Peripheral airway function in adults with sickle cell disease is not associated with increased risk of infection.
PI1185
Assessment of tracheobronchomalacia in relapsing polyrhondritis using impulse oscillometry
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Results: Five patients developed into tracheobronchomalacia (TBM). R5-R20 and X5 showed a significant difference between patients with TBM and patients with only airway involvement (AI) (R5-R20/TBM 0.48±0.21kPa/l/s, AI 0.15±0.27kPa/l/s, p<0.005, X5: TBM -0.48±0.17 kPa/l/s, AI -2.2±0.25 kPa/l/s, p=0.013). IOS was measured before and after stenting in 1 patient and a marked improvement was seen after stenting (before: R5 0.95kPa/l/s, R20 0.5kPa/l/s, 0.66kPa/l/s, R5-R20 0.05kPa/l/s, after: R5 0.31kPa/l/s, R20 0.29kPa/l/s, 0.09kPa/l/s, Freq 9.13 Hz, R5-R20 0.02kPa/l/s).

Conclusions: IOS was useful in the evaluation of airway involvement in RP and R5-R20 and X5 were practical markers to differentiate patients with TBM.

PI1186
Diagnostics of loss in lung elastic recoil pressure using impulse oscillometry and body plethysmography
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Respiratory resistance at 20 Hz (R20) by impulse oscillometry (IO) characterizes airways resistance with inextensible walls. Airways resistance (Rtot) by body plethysmography reflects the total resistance of the first 8 - 10 bronchi generations. These indicators by different methods are close physiologically. The airways in patients with an emphysema are deprived of elastic support, so a lung compliance (CL) considerably increases. We have assumed that shortening of R20 increases with loss of lung elastic recoil.

Aim of the study is evaluation loss of respiratory resistance by IO with increasing of compliance and decreasing of lung elastic recoil.

Methods and materials: We compared Rtot and R20 in 67 healthy volunteers (32F/35M, 47±1 yrs) and in the patients with obstructive disorders - 41 patients with COPD (16F/25M, 56±1 yrs) and 52 patients with bronchial asthma (34F/18M, 47±2 yrs). We have used the relation Rtot/R20. All patients were performed investigation of lung elasticity using esophagus balloon.

Results: Rtot/R20 in healthy group was 0.79±0.03 and in patients with obstructive disorders it was 1.72±0.10 (p<0.01). The analysis Rtot/R20 in patients with obstructive disorders showed considerable difference of Rtot/R20 value in patients with normal lung elastic recoil and in patients with loss lung elastic recoil (1.24 and 2.08 respectively, p<0.01). The correlation analysis showed moderate dependence Rtot/R20 with CL and coefficient of retraction (CR) (r=0.57 and 0.38 accordingly, p=0.01).

Conclusion: The relation Rtot/R20 reflects loss in parenchymal elastic recoil pressure. In healthy and patients with obstructive disorders with normal lung elastic recoil it is less 1.24.

PI1187
Direct airway resistance response after deep inspiration in symptomatic asthmatics
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Introduction: Immediately after a deep inspiration there is a response in the airways resistance. In patients with asthma the response to deep inspiration (DI) is impaired compared with healthy subjects.

Aim: We want to investigate the airway resistance response after DI changes when subjects are exposed to a bronchoconstrictor.

Methods: All subjects were symptomatic asthmatics. They all performed a tidal breathing challenge test (Meth) with methacholine bromide from 0.039-39.6 mg/ml in doubling doses. After each inhalation the airway resistance was measured by impulse oscillometry (IOS/PFT, Care Fusion, Würzburg) during 60-80 seconds with a DI at 30s. At 90s FEV1 was measured. P-values <0.05 were assumed to be significant.

Results: We analyzed 24 tests. One patient was excluded because of spirometric induced asthma. In 12 cases we found a PC20 <16 mg/ml. In 11 patients there was no PC20 or a PC20 >16.

P20±16 p-value
mean at baseline
R5 (kPa/l/s) 0.37 0.28 0.072
R5-R15 (kPa/l/s) 0.08 0.06 <0.05
ΔR5 0.08 0.06 <0.05
ΔR5-R15 0.004 0.000 <0.05

At mean at baseline
R5 (kPa/l/s) 0.66 0.45 0.005
R5-R15 (kPa/l/s) 0.26 0.15 0.038
ΔR5 0.08 0.04 <0.05
ΔR5-R15 0.03 <0.05

ΔR5 is the difference in R5 before and after DI, ΔR5-R15 is the difference in R5 before and after DI. We found a significant difference in ΔR5 between baseline and the highest concentration both in cases and non cases (resp: p<0.024 and p=0.022).

Conclusion: When PC20 is reached there is still an overall decrease in airway resistance after DI. Compared to those who didn’t reach PC20 <16 the decrease is not significant but both groups had a high SE. The response to DI is highly variable in asthmatics.

P1189
Agreement of airway resistance measurements by two different techniques of body-plethysmography and impulse oscillmetry in asthmatic patients
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Background: Airway resistance can be measured by different techniques of body-plethysmography and impulse oscillometry (IOS). So far there has been no systematic study comparing validity of these techniques in relation to clinical condition of the patients reported.

Aims and objectives: We investigated correlation between these techniques in assessment of airway resistance and asthma control test.

Methods: In 92 patients with asthma selected on the basis of ATS criteria for diagnosis of asthma and GINA asthma control test (ACT) questionnaire completed. Pulmonary function tests including body-plethysmography with airway resistance measurement and impulse oscillometry measuring total airway resistance at 5 Hz and 20Hz were done using IOS.

Results: ACT score has a significant correlation with a r value of - 0.34 with total airway resistance measured by body-plethysmography (p=0.003) and also significant correlation with r value of - 0.31 (p=0.002) with airway resistance measured by IOS at 5Hz but no significant correlation with airway resistance measured by IOS at 20 Hz. There is a significant correlation between airway resistance measured by body plethysmography and airway resistance measured by IOS at 5 Hz and at 20 Hz.

Conclusions: These finding indicates a good correlation of total airway resistance measured by body plethysmography and by IOS at 5 Hz as well as at 20 Hz which is stronger with the first. Also significant negative correlation between ACT score and airway resistance centered in peripheral airways measured by IOS at 5 Hz but not with the resistance at central airways measured mainly by IOS at 20Hz.

P1198
Sgaw as an alternative for FEV1 in the measurement of airway responsiveness to methacholine in patients experiencing chronic cough
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Background: A drop of 5% in specific airway conductance (S Gaw) during a methacholine challenge test (MCT) is considered to be comparable to a drop of 20% in FEV1 to assess airway hyperresponsiveness (AHR). In our department patients with chronic cough tested with a MCT on a drop of FEV1 show an increase in cough without reaching a conclusive PC20.

Aim: To examine the correlation between drops in FEV1 and S Gaw during MCT in chronic cough patients.

Methods: 16 patients with history of chronic cough were included for a cross-sectional study. Inclusion criteria: episodic chest symptoms, chronic cough and post bronchodilator FEV1/FVC ratio ≥ 0.70. Each concentration in MCT was followed by measurement of S Gaw and FEV1. Linear regression was used to determine the correlation between PC20 FEV1 and PC50S Gaw.

Results: LogPC50S Gaw was significantly lower than log PC20FEV1 (p<0.004). 7 patients showed a positive response only to S Gaw (Figure 1).

We found that a decrease of 20% in FEV1 was accompanied by 65% decrease in S Gaw.
Conclusions: Patients with chronic cough show a larger response to methacholine by sGaw as compared to FEV1 than reported in the literature. This suggests that in this set of patients sGaw is relatively more sensitive in assessing AHR.

Implications: Chronic cough patients may exhibit AHR that remains unnoticed when performing MCT with FEV1.

P1190
Non-invasive measurement of respiratory impedance in conscious guinea pigs utilising impulse oscillometry
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Aim: Since rodents are often utilised as models in respiratory research, we investigated a newly constructed Impulse Oscillometry System (IOS) which was modified to allow non invasive measurements of respiratory impedance in conscious guinea pigs.

Material and methods: Five female guinea pigs (body weight 592.2±73.0 g) were included in the study. The animals were fixated manually in an extended supine position. a) Three consecutive IOS measurements, taken within a few minutes duration from each animal were used to evaluate short time variability. b) The results of measurements taken on three consecutive days at the same time of the day were used to assess long time variability. Coefficients of variation (CV%) were calculated for oscillometric resistance parameters between 5 and 35 Hz.

Results: Coefficients of variation (CV%) for Resistance parameters at selected frequencies are shown in table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study A</th>
<th>Study B</th>
</tr>
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<tbody>
<tr>
<td>R5</td>
<td>6.9±0.6</td>
<td>11.5±1.5</td>
</tr>
<tr>
<td>R10</td>
<td>7.1±0.8</td>
<td>13.6±2.8</td>
</tr>
<tr>
<td>R15</td>
<td>6.1±2.1</td>
<td>10.5±1.6</td>
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<tr>
<td>R20</td>
<td>5.3±2.3</td>
<td>8.9±2.0</td>
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<tr>
<td>R25</td>
<td>3.4±2.3</td>
<td>5.5±2.6</td>
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<tr>
<td>R30</td>
<td>2.7±1.6</td>
<td>3.2±2.0</td>
</tr>
<tr>
<td>R35</td>
<td>3.1±1.0</td>
<td>2.3±1.2</td>
</tr>
</tbody>
</table>

Conclusion: Putting awake guinea pigs in supine body position they get into a sleep-like condition. This was the preferred procedure to get well reproducible results of impedance spectra utilising impulse oscillometry in this species.

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P1192
Appropriateness of ATS/ERS recommended lung volume reference values for contemporary Australasian children
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Introduction: There are only limited reference ranges for static lung volumes (LV) by Plethysmography (PLETH) or gas dilution (DIL) that encompasses the paediatric age range. International recommendations suggest the data from Zaplateel (PLETH) and Cook (DIL) be used pending appropriate data using modern equipment and most recent guidelines.

Aim: To assess the suitability of these recommended reference ranges to contemporary healthy Australasian children.

Methods: Healthy subjects performed LV measurements by DIL or PLETH according to the 2005 ATS/ERS guidelines. Data was compared to recommended reference ranges and expressed as% predicted.

Results: Measurements were obtained in 244 subjects aged 5 to 19 years (120 male) of which 121 and 144 performed LV by DIL and PLETH, respectively.

Lung volumes as %pred

<table>
<thead>
<tr>
<th></th>
<th>DIL (Cook % pred)</th>
<th>PLETH (Zaplatel % pred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>mean</td>
<td>range</td>
</tr>
<tr>
<td>FRC</td>
<td>121</td>
<td>91.9</td>
</tr>
<tr>
<td>TLC</td>
<td>117</td>
<td>97.2</td>
</tr>
<tr>
<td>RV</td>
<td>113</td>
<td>80.5</td>
</tr>
</tbody>
</table>

FRC and RV measured by both methods were significantly lower than published values (p<.001). Individuals below the LLN for TLC and outside the 95% CI for FRC and RV ranged from 4% for TLC by DIL to 55% for RV by PLETH.

Conclusions: Measured TLC agrees well with both PLETH and DIL reference ranges. FRC and RV by either method were significantly lower than predicted. A proportion of these healthy subjects would be considered to have LV outside the normal range. The recommended reference ranges for RV and FRC are inappropriate for use in Australasian children. New reference ranges using modern equipment are needed for this population.

P1193
Spacer device selection may not impact bronchodilator responsiveness (BDR) in asthmatic children
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Assessment of spirometry before and after bronchodilators is used in the diagnosis and management of asthma. The impact of spacer device selection on clinical BDR is poorly understood. ATS guidelines state 400μg of salbutamol should be used for BDR testing. The aim of this study was to investigate if spacer selection has an effect on BDR in asthmatic children and at what salbutamol dose BDR reached significance.

Methods: This study compared spirometry and BDR with a disposable spacer (Lite Aire; Thayer Medical) and a multi-patient use spacer (Space Pod; Medical
P1194 Feasibility and reproducibility of pulmonary function tests in preschoolers

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Relevance: Preschoolers present particularities that reinforce the importance of assessing their pulmonary function; however few studies have focused on pulmonary function tests in this population.

Purpose: To assess the feasibility of assessing breathing pattern through inductive respiratory plethysmography, spirometry and peak cough flow (PCF) in healthy preschoolers, as well as the test-retest reproducibility of these tests.

Methods: It was assessed the breathing pattern (tidal volume-Vt; respiratory frequency-f; inspiratory time -Tl; inspiratory duty cycle-Tl/Ttot, mean respiratory flow -Vm; peak and root mean-square (RMS) of bronchial flow), spirometry (forced vital capacity-FVC, forced expiratory (min) volume forced in one second (FEV1), FEV1/VC and FEV1/VC and PCF and 38 healthy children aged 4.8±0.6 years. To evaluate the test-retest reproducibility, 10 children (depending to sample size calculation) were reassessed after three weeks. The study was approved by Ethics Committee. Feasibility was defined as the rate of success achieved by the children. Test-retest reproducibility was evaluated by paired t-test, considering significant p<0.05, and Intraclass Correlation Coefficient (ICC).

Results: The results showed a rate of successes of 100% for breathing pattern, 84% for spirometry and 90% for PCF. Regarding the reproducibility, there were no significant differences between variables of any test and it was observed the following ICC values: Vt=0.74, f=0.87, Tl=0.80; Tl/Ttot=0.95, Vm=0.68; 4.6%. ICC of 0.66, FVC=0.92, FEV1=0.81, FEV1/VC=0.75, PCF=0.85.

Conclusions: These results suggest high rate of success in performing the pulmonary function tests and good test-retest reproducibility in healthy preschoolers.

P1195 Feasibility of spirometry-controlled chest magnetic resonance imaging (MRI) in children

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Standardization of inflation- and expiration level using a spirometer during chest-MRI is important to optimise image quality and interpretation. To perform the correct breathing manoeuvres in a MRI is a challenge for most children.

Aim of this pilot study: To evaluate the feasibility of spirometry-controlled chest-MRI.

Methods: A custom made MRI compatible spirometer (Masterscope, Carefusion) and a dedicated holder for the spirometer head was used. This allowed correct and child friendly positioning of the spirometer in the MRI.

Children practiced in supine position 4 hour prior to MRI with a lung function technician the following breathing manoeuvres: slow vital capacity (SVC); a breath-hold (13 sec) at Total Lung Capacity and at Residual Volume; and flow volume and coughing to obtain dynamic images of central arteries. During the MRI the lung function technician sat by site by the MRI technician and coached and monitored the child’s performance and instructed the MRI technician when to start the acquisition.

Results: 14 Children (age 5 – 17 years, 9 boys) had a MRI. Each child was able to perform the child prior to the MRI and coach the child during the MRI by a lung function technician.

Conclusion: Spirometry-controlled chest MRI is feasible in most children and improves the standardization and the image quality of chest MRI. We recommend training of the child prior to the MRI and coaching of the child during the MRI by a lung function technician.

P1196 Early lung function testing in infants with aortic arch anomalies identifies infants at risk for airway obstruction

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Aortic arch anomalies (AAA) (vascular rings) are rare anomalies (approx. 3% of all cardiac anomalies) that can obstruct the upper airway. The preferred strategies for diagnosis and treatment vary among institutions. The aim of this study was to investigate the degree of airway obstruction in infants with AAA by lung function testing (LFT).

Patients and methods: Sixteen patients born between 2005-2010 with echocardiographic: AAA (10 right sided (69%) and 6 double aortic arch (31%)) preoperative LFT was performed in the 39th (36th – 41th) postconceptional week (median (range)) body weight 3300 (2320 - 4360) g. Raw was measured by baby bodyplethysmography (Jaeger, Wurzburg, Germany). With the same equipment the maximal expiratory flow at functional residual capacity (V’maxFRC) was measured using the rapid thoraco-abdominal compression (RTC) technique, according to international guidelines. V’maxFRC was also expressed in standard deviation scores (Z-scores) based on sex-, age and high-specific reference values of healthy infants published by Hoo et al. AJRCMB 2002.

Results: Between Raw and the Z-score of V’maxFRC was a strong correlation (r=0.768, p<0.001). Most infants were within the normal range of V’maxFRC without statistically significant difference between right sided and double AAA. However, 3 infants (20%) were near or distinctly below the 10th percentile of V’maxFRC and had Raw >-1.41zH2O/L/s, indicating upper airway obstruction.

Conclusion: Most infants with AAA had no impairment of the upper airway conductivity. However, early LFT may help to indentify and to monitor patients who may be at risk for significant airway obstruction.

P1197 Forced expiratory tracheal noise time in diagnostics of hidden bronchial obstruction among spirometry negative asthma patients

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Computer instrumentation (Korzenbaum et al., 2008) provides a precise estimation of acoustic tracheal forced expiratory noises time (FETa). The purpose was an estimation of FETa efficiency as diagnostic test of hidden bronchial obstruction (BO). The sample consisted of homogeneous groups: young male asthma (BA) patients as a BO model (71 persons with spirometry negative BO), control group (77 non-smoking healthy subjects and 44 smokers). FETa values were normalized by C – chest circumference, H – height, M – body mass. The FETa was divided by ROC-analyzis. Percentages of deviation from the norm, revealed by acoustic indicators in groups were evaluated.

Conclusions: The presence of BO in healthy non-smokers patients with spirometry negative is 0.01 re healthy non-smokers.

Diagnostic efficiency of FETa and its normalized indicators in spirometry positive BA is very close to efficiency of base-line spirometry. Moreover, bronchial obstruction is acoustically diagnosed almost in a half of patients with spirometry negative BA, whereas healthy are indistinguishable from young smokers. Thus, FETa seems to be important for diagnostics of hidden bronchial obstruction, at least, in young male subjects. The study was supported by Far Eastern Branch of Russian Academy of Sciences grants No. 09-1-P21-08, No. 09-3-A-06-231.

P1198 Dynamic hyperinflation in patients with severe COPD

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Introduction: Dynamic hyperinflation (DH) is thought to be an important clinical feature in patients with COPD, but is difficult to measure.

 Aim: To investigate DH in patients with COPD referred for bronchoscopic lung volume reduction and to test the feasibility of using metronome paced hyperventilation (MPH).

 Methods: DH was measured by MPH using the breath-by-breath method (Oxycon Pro) in a 15-min protocol. After 3 baseline IC maneuvers, 3 MPH tests (40Hz for 60 sec, with 3 min rest in-between) were performed. Each MPH test was directly followed by an IC maneuver. DH was defined as IC/IC (decrease in IC/baseline IC) and calculated using the average of 3 ICs.

Groups Healthy patients non-smokers BA smokers BA patients with approved BO

FETa 16 27.3 41* 78.9* 78.9*
FETa/C 17 25 49.2* 87.8* 87.8*
FETa/H 18 27.3 47.4** 80.3* 80.3*
FETa/M 13 22.7 46.2* 83.9* 83.9*
FETa/VFRC >75% 2.6 0 0 74.6* 74.6*

*p<0.001; **p<0.01 re healthy non-smokers.

218s
Conclusion: All patients tolerated the MPH very well. IC variability was 4.6% (±4.0), and 8.6% (±4.4) after MPH. VE reached 28.8 L/min (±12.6), calculated maximal VE (FEV1% ±7.5) was 34.5 L/min (±15.5). MPH frequency was 39.7 Hz (±1.4). For the Gold-IV patient group the IC of 1.83 L (±0.47) decreased to 1.21 L (±0.42) after MPH with a ΔIC/IC of 34% (±12). In Gold-III IC decreased from 2.39 L (±0.93), to 1.79 L (±0.63) with a ΔIC/IC of 23% (±12). In the overall group ΔIC/IC correlated with TLC-He (r=0.45, p=0.03) and FEV1 (r=-0.38, p=0.04).

Conclusion: Measuring DH is feasible using MPH, and can be used in the routine clinical setting. DH is significantly present in patients with COPD and increases with disease severity.

Results: Good agreement was found between phase delay estimated by ACC and SI (r =0.98, p<0.001; Figure, panel a). Mean values were 219 s and -0.45 with delays at AUR significantly smaller than ALRI (r =0.985±0.2262 vs -1.941±0.2655; p=0.0002).

Discussion: The results show that novel methods for CO measurement in exhaled air can be used for non-invasive monitoring of CO exposure. The proposed method is simple, rapid, and requires no specialized equipment. It can be used in various clinical settings, including health monitoring, occupational health, and environmental exposure assessment. Future studies should focus on optimizing the sensitivity and specificity of the method for different CO sources and exposure scenarios.
P1203

Static lung volumes in lung transplant recipients with bronchiolitis obliterans syndrome
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The bronchiolitis obliterans syndrome (BOS), post lung transplantation, is defined as progressive, irreversible obstruction of the small airways leading to pulmonary hypertension and declining lung function. We studied 32 patients: post SLT and post sequential single lung transplantation (SSLT).

We studied 32 patients: 11 SLT (9 COPD; 2 OB) and 21 SSLT (6 COPD; 1 OB; 14 cystic fibrosis). The SSLT group were significantly younger (median 38 ± 5 years).

SLT median 52.8 ± 72.8 121 ± 156 0.48 1.64 0.77
SLT range 30.5-64.1 51.4-88.2 90.9-179.0 102-175 0.62-0.81 0.93-3.49 0.45-0.95

SSLT median 63.3 ± 82.6 89.9 ± 101 0.63 2.0 0.60
SSLT range 30-1-30.10 52.2-110 53.1-124.0 72.8-164.0 0.51-0.77 0.96-3.29 0.39-0.79

The SSLT group had larger TLC and FRC, while IC was similar in the two groups and, as a proportion of VC, was actually greater in the SLT group.

IC was relatively well preserved in the SLT patients with early BOS, despite the presence of a hyperinflated native lung. Longitudinal lung volume measurements might usefully evaluate the progress of BOS in both SLT and SSLT recipients.

P1204

Postoperative predictive value of lung function in patients with lung cancer – Fortune-telling or reality? Evaluation after surgical treatment
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Lung function testing is important tool of the evaluation patients with lung cancer, candidates for surgical treatment. Based on the scope of the planned resection and the result of bronchofiberoscopy there is possible to calculate the expected postoperative value of lung function (ppoFEV1, pppoLCO), but reliability of such estimation is still under discussion. The aim of the study was to evaluate lung function in the postoperative out-patient observation and compliance with the result.

The analysis included 42 operated pts (mean age 64.3 ± 8.8 yrs, 23 M) who underwent spirometry before resection and after 3 and 6 months during the out-patient follow-up. The people undergoing additional chemotherapy and/or radiotherapy were excluded from the assessment.

Lobectomy was performed in 39 pts (28 upper, 11 lower) one pneumonia in 3 pts. Mean FEV1 value before surgery and 3 and 6 months after was 2.36±0.49 L (88.0±18.3%), 1.79±0.45 L (67.2±18.6%) and 1.84±0.47 L (68.9±18.1%) respectively. The significant correlation of pppoFEV1 (1.9±0.55 L, 73.1±18.3%) and measured values was revealed, amounting to 0.72 and 0.76 respectively for the study in 3 and 6 months after surgery. Detailed analysis showed that the correlation was higher in group of patients after lower than upper lobectomy: 0.85 vs 0.73 at 6 months after resection.

Conclusion: In studied group mean value FEV1 measured in the postoperative follow-up at 3 and 6 months after resection shown good agreement with pppoFEV1, however better for patients who underwent lower lobectomy, poorer for upper resection.

P1205

Maximal inspiratory pressures, lung volumes and flows in young rowers
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Respiratory muscle training has demonstrated improvement in exercise performance in both healthy adults and in patients with chronic respiratory illnesses. Such programs often ask to perform respiratory efforts against a pressure load equivalent to a certain percent of maximal respiratory pressures. Portable devices are available to measure those maximal pressures, but it can be highly dependent on participant effort.

Our aim was to find out whether maximal inspiratory pressure (MIP) correlates with different flow-volume loop parameters in a group of college level rowers and to compare the data from athletes with reference values.

We studied 19-33 year-old rowers (n=14, two of them female) with height 173-202 cm. Spirometry was performed to determine FVC, FEV1, PEF and PIF. MIP was measured with a hand-held mouth pressure meter. All measured values were compared with reference data and correlations between MIP lung function and anthropometric indices were found.

Compared to reference population values of FVC and FEV1, from rowers were mostly above average (97-130% pred.), whereas PEF ranged from 85 to 126% of predicted. All 3 forced expiration indices correlated with height (r=0.01). When using MIP reference values depending on age only, we obtained values in a range of 88-212% pred (absolute values 98-234 cm H2O). The only significant positive correlation was found between MIP and PIF (r=0.05).

Relatively high lung volumes and flows compared to the predicted values indicate the increased functional capacity of respiratory system in rowers. We found a wide range of MIP values in young subjects with MIP and PIF did correlate with neither anthropometric nor spirometric indices (except for PIF).

P1206

Asthma diagnosis by the reversibility test of respiratory muscles power in asthmatics using the respiratory pressure meter
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Introduction: Intermittent and mild asthma types are difficult to diagnose during the symptoms free period. The respiratory muscles perform extra work in asthma and expected to be stronger than normal subjects. The respiratory pressure meter measures the respiratory muscle power as a function of the air volume expired or inspired by effort. The hypothesis was introduced that if the bronchiodilators are dilated by a bronchodilator the expired volume of air and consequently the pressure it exerts is expected to increase.

Objective: To perform a pilot reversibility test in asthmatic patients by spirometry and respiratory pressure meter.

Methods: This is a cross-sectional hospital based study carried out in Lung function tests clinic in Police hospital in Khartoum in 2010 –2011 to determine the reversibility of the respiratory muscle power after salbutamol inhalation using the respiratory pressure meter. Following informed consent, PEFR, FEV1/FVC, Maximum inspiratory pressure (MIP) and Maximum inspiratory pressure (MIP) were measured in 20 patients with asthma and the tests were repeated 15 minutes after salbutamol inhalation. All patients were not during an acute attack.

Results: 20 patients were included. FEV1 reversibility was 10.8% and PEFR reversibility was 13.1%. The MIP increased from 81.2 cmH2O to 91.2 cmH2O, with a reversibility of 12.3% while the MIP increased from 60.8 to 69.9 cm H2O, with a reversibility of 15%.

Conclusion: Respiratory muscles power reversibility could be a potentially sensitive diagnostic test for asthma.
FEV1 values were 4.1% larger than the predicted values in the whole group. For 31 subjects (58.5%) measured FEV1 values were outside the 95-105% interval of FEV1 predicted values.

Conclusions: A significant number of healthy adults have had spirometric values outside the confidence interval of predicted values (European equations in use). A larger study is needed in subjects with different ages and heights to verify the data obtained in our study. The opportunity of determining specific predicted values in a large population study is discussed, considering the necessary resources.

P1208
E-patient reported outcomes: Can you have reliance on compliance?
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Introduction: Consistent evidence is required to confirm the value of electronic Patient Reported Outcomes (e-PROs) for compliance in Usage and Quality of PEF manoeuvres in large clinical trials where these data are used as critical end-points [1].

Method: In an international asthma trial requiring twice daily symptom scores and three PEF manoeuvres over 105 days e-PROs were recorded using the Vitalograph PEV/PEF e-diary within a protocol specific program. Usage Compliance was assessed by the actual number of completed sessions made by patients as a percentage of the potential total. Quality Compliance assessed by Repeatability of the two highest manoeuvres of a session using the ATS/ERS standard of ≤3±3L/min.

Results: From 519 asthmatic patients at 78 sites a total of 103,198 diary sessions were made. Compliance during screening was 93.7%, treatment 88.4% and overall 89.8%.

Three manoeuvres were recorded in 99% of the sessions.

Repeatability Compliance of PEF for both screen and treatment periods was 88%. The difference in PEF between the two highest manoeuvres was 13.8±3 L/min.

There was no statistical difference between the morning and evening data.

Conclusion: These data concur with other previously published [2]. Thus e-PROs from asthmatic patients are consistent for both quantity and quality and have statistical reliance as the primary end-points for future trials.

References:

The sponsors of this trial are thanked for the anonymous use of their data.

P1209
Comparison of referral patterns between a respiratory laboratory in the Republic of Ireland and Western Australia
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Background: Respiratory diseases account for 13% of deaths in the Republic of Ireland (ROI), and 8% in Western Australia (WA) each year. County Cork has a population of 0.5 million and is served by Cork University Hospital (CUH), one other public, and one private hospital laboratory. CUH has 815 beds and is the principle teaching hospital. Located in the city centre, Royal Perth Hospital (RPH) is the largest teaching hospital (855 beds) in WA, which has a population of 2.2 million. This area is also serviced by three other teaching hospitals, and numerous private laboratories.

Diagnosis | CUH | RPH |
--- | --- | --- |
Asthma | 12.8% | 10.1% |
COPD | 16.9% | 20.3% |
ILD | 22.7% | 10.3% |
CF | 7.5% | 0.8% |
Cancer | 5.5% | 9.5% |
Connective tissue | 5.7% | 6.4% |
Other | 27.4% | 17.7% |
Not specified | 1.6% | 24.9% |

Test | CUH | RPH |
--- | --- | --- |
Spirometry | 2811 | 3054 |
DLCO | 1350 | 1266 |
Lung volumes | 1119 | 1208 |
Mouth pressures | 41 | 39 |
CPET | 5 | 35 |
Altitude simulation | Test not offered | 53 |
Skin allergen | | |
6 MWD | Physiotherapist role | 88 |
Bromchial challenge | 6 | 5 |
Total | 5360 | 5766 |

Aim: To compare test request profiles of two public respiratory laboratories in ROI and WA.

Method: Referrals to each laboratory between 1st November 2009 and 31st October 2010, were reviewed.

Results: CUH performed 5360 tests on 2104 patients, aged 5-90 years. 9% were repeat visits within the time frame. RPH performed 5766 tests on 2336 patients, aged 13-98 years. 14% were repeat visits. The results offered and diagnoses are presented.

Discussion: The number of patients seen, and number of tests per patient were comparable. Specialist nurses at CUH perform spirometry which is redirected in the reduced number of COPD and cancer patients seen in the laboratory.

P1210
How to diagnose restrictive ventilatory defect by spirometry, and reduce the number of lung volumes measurements?
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Diagnosis of restrictive ventilatory defect by a low FVC on spirometry is not accurate, even in non-obstructive patients. On the other hand TLC measurements are time-consuming and expensive. So it would be convenient to be able to predict or rule out the possibility of restrictive defect by spirometry and reduce the number of unnecessary TLC measurements.

Aim of the study: We have looked for a FVC value above which reduced TLC is very unlikely, and other FVC value below which it is highly probable.

Material: Consisted of pulmonary test results obtained from adult patients, who had undergone spirometry and lung volumes measurements at the same visit.

Results: From the whole 6538 test results, 4089 patients (53.2% females, 46.8% males; mean age 47.5±14.9 years) without airway obstruction were included into analysis. Restrictive ventilatory defect (TLC <50th percentile) was found in 955 (19.5%) patients, and reduced FVC (FVC <5th percentile) was found in 655 (13.4%) patients. Setting arbitrary the lower limit on 70% of FVC pred. to predict volume restriction had specificity 99%, and PPV 91%. Setting the upper limit at 95% of FVC pred. to exclude volume restriction had NPV 99%. Performing TLC measurements only in patients with FVC between 70 and 95% of pred., would reduce number of tests by 2/3 to 1/3.

Conclusions: Spirometry allows accurately rule out volume restriction in patients with FVC >95% of pred., and predict restrictive defect in patients with FVC <70% of pred. Performing TLC measurements only in patients with FVC between 70 and 95% of pred. reduces the number of tests and costs of diagnosis of restrictive defect.

P1211
Non invasive assessment of pulmonary shunt in adults with liver disease
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Introduction: The oxygen dissociation curve charts the relationship between haemoglobin saturation (SaO2) and arterial pO2. Less well known is the relationship between the inspired oxygen (FiO2) and SaO2, which reflects aspects of the oxygen cascade that affect the transfer of oxygen into blood.

A number of models describe this cascade and this allows reconstruction of the curve from a number of data points, allowing estimation of the shunt and whole lung VQ ratio. Its value lies in the simplicity with which both FiO2 and SaO2 can be measured.

We are undertaking a “proof of concept” study evaluating shunt in adults undergoing assessment for liver transplantation, where pulmonary shunt is an important clinical problem.

Methods: Adults breathe an O2:N2 mix with an FiO2 between 0.14 and 0.35. After equilibration, SaO2 is recorded. At least 3 data points are collected, and analysed using previously validated methodology [1] recently adapted for MATLAB.

Results: To date (February 2011) we have studied 9 patients with this technique. All tolerated the procedure well. Studies were performed in our respiratory laboratory and took between 20 and 30 minutes to complete.

Shunt varied between 2% and 20% and VQ ratios between 0.78 and 1.5. Patients are also having shunt assessed by VQ scans, and these data will be compared.

Conclusions: This technique offers a very simple and well tolerated test that quantifies both shunt and VQ mismatch. It only requires an oximeter and a supply of nitrogen. Given that current methods for assessing these parameters require specialised equipment and are time consuming, it may provide an effective test for shunt or VQ matching in a wide range of patients.

Reference:

SUNDAY, SEPTEMBER 25TH 2011

F221s
P1212

Is obstructive lung disease correlated to age and smoking habit or is there more?
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Background: On World Spirometry Day lung function measurements were done to identify obstructive patients without a previous diagnosis of an obstructive lung condition and to raise awareness on lung health and disease.

Aim: To establish the significance of the degree of obstruction in relation to reported symptoms and other characteristics.

Methods: 783 participants performed lung function and filled a standard questionnaire. The degree of obstruction in relation to smoking, shortness of breath, cough, age and BMI were investigated. Significance in relationships was measured with multivariate analysis with backward elimination.

Results:

In 15.8% an abnormal lung function was measured: 124 times obstruction based on FEV1/FVC and another 43 cases with a FEV1 below 80%.

In a linear regression model smoking (β = 0.015 p < 0.005) and age (β = -0.02 p < 0.005) were significant predictors in obstruction.

Conclusions: There was a positive correlation between age and smoking but no correlation with other characteristics. Amongst the older obstructive participants there is a large group of non-smokers who need further investigation.

Implications: In its current form the WSD cannot identify persons at risk for an obstructive lung disease. In case of a low FEV1 and/or a low FEV1/FVC the test should also be repeated after a bronchodilator. There has to be a good description of the target group and a questionnaire adapted to the group.

P1213

The correlation between lung function parameters, and level of activity in seropositive rheumatoid arthritis
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Pulmonary involvement is one of the most frequent extra-articular manifestation of rheumatoid arthritis.

Aim: To assess the lung function (LFT) and diffusion capacity (DLCO) in non-smoker patients with rheumatoid arthritis (RA) and correlation with disease activity and rheumatoid factor positivity.

Methods: 55 patients non-smokers with a prior diagnosis of RA in rheumatology department, were subjected to lung function analysis. The various parameters - from spirometry, diffusion capacity, -were correlated with rheumatoid factor (RF) positivity (RA+/-) and disease activity score (DAS), C reactive protein (CRP) levels.

None of them had the diagnosis of lung interstitial disease prior the study.

Results:

30.9% had negative rheumatoid factor, and 69% positive; from them 12.7% were male;
FEV1, FVC, TLC were lower in RA+ group than in RA- and FEV1/FVC was higher in RA+ group (81.4% vs. 126.2%). Statistical significance was achieved for FEV1/FVC and TLC (4.6 vs. 1.6).

TLCO was lower than predicted values in 36.4%; 29.4% in RA- and 39.8% in RA+ (OR=1.4); corrected TLCO was 22.3 ± 4.8 in RA+ and 20.1 ± 3.6 in RA- (p=0.03) regarding level of activity, decreased TLCO was correlated (correlation factor=0.29) with RF positivity, CRP high levels (>8.9) and high DAS (>4.8).

Restrictive dysfunction had 23.6% RA+ (OR=2.5)and 11.7% RA- Decreased TLCO had 63.6% from those with restrictive dysfunction (71.4% in RA+ group). More than 50% from those with restrictive dysfunction and low TLCO had a DAS ≥5.

Conclusions: Restrictive dysfunction and decreased TLCO are correlated with RF positivity and with high level of disease activity in patients with RA.

P1214

Assessment of the suitability of filters for use in clinical studies with an HFA fluticasone propionate pressurized metered dose inhaler (pMDI) and a valved holding chamber (VHC)
Kurt Nikander1, Lois Slator2, Dirk von Holten1, Ross Hatley2. 1Philips Respironics, Respironics New Jersey, Inc., Parrygall, NJ, United States; 2Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, United Kingdom

The assessment of delivered dose is an integral part of the development protocol for new aerosol delivery devices, especially in pediatric patients in which pharmacokinetic studies are difficult to perform.

The aim of this study was to evaluate the dose collection efficiency of a 3 M Filterte G-200 (G-200) filter in a low dead space filter holder for use in ex vivo testing using a preproduction OptiChamber Diamond VHC (Diamond; Philips Respironics). Two preproduction Diamond VHCs were tested over 10 runs. Five fluticasone propionate (Flonfenta HFA 220 μg) pMDIs were primed before use. The mouthpiece of the VHC was sealed to a filter holder containing two 67 mm G-200 filters. The pMDI was actuated into the VHC, followed by 20 s extraction (at 90 L/min), repeated 25 times. Filters and VHC deposits were analyzed using HPLC (Agilent 1100/1200). The percentage of total emitted dose deposited on the 2nd filters over 10 runs was calculated; where the amount of drug detected on the 2nd filter was below the Limit of Quantification (LOQ; 25 μg) the LOQ was used to calculate the total, and where the amount detected was zero the Limit of Detection (LOD; 2.5 μg) was used to calculate the total (overestimates the total amount on the 2nd filters significantly), the total was then divided by total recovered drug.

Desaturation during maximal exercise can be caused by several problems; decreased diffusing capacity, leading to an increased Alveolar-arterial problems; decreased diffusing capacity, leading to an increased Alveolar-arterial

Discussion: Despite the correlation and agreement between two methods for measuring inspiratory capacity, they can have significant variability within and between methods.

P1216

Can NO diffusion predict desaturation during maximal exercise?
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Introduction: Desaturation during maximal exercise can be caused by several problems; decreased diffusing capacity, leading to an increased Alveolar-arterial (A-a) oxygen gradient, or V/Q mismatch or a contact time problem. The present method to establish decreased diffusing capacity is the measurement of diffusing capacity for carbon monoxide (TLCO). We hypothesise that the diffusing capacity for nitric oxide (TLONO) is more accurate than TLCO.

Aim: The aim of this study is to find out whether diffusing capacity for NO, as a marker for the membrane component of diffusion, can be a more accurate predictor of the A-a gradient at maximal exercise, compared to diffusing capacity for CO, as a marker for the membrane and hemodynamic component of diffusion.

Methods: 15 patients with pulmonary complaints (mean age 38 years) performed a combined single breath TLONO/TLCO measurement and a maximal exercise test.

We constructed a model to predict the A-a gradient at maximal exercise.
Results: The A-a gradient at maximal exercise can be predicted by TLCO%R, and resulted in an R^2 (coefficient of determination) of 0.64. TLNO%R predicted the A-a gradient at maximal exercise with an R^2 of 0.81 (see figure).

Conclusion: The diffusing capacity for NO is a more accurate predictor of the A-a gradient at maximal exercise than the diffusing capacity for CO, and thereby a more accurate predictor of desaturation during exercise.

Reference:

P1217
DLno; slave to a rhythm?
Antoinette Houtkooper, P.J.A.M. van Ooij, R.A. van Hulst. MMEC - Diving Medical Center, Royal Netherlands Navy, Den Helder, NH, Netherlands

Background: It is generally accepted that spirometry and diffusing capacity are subjected to a diurnal rhythm (CINKOTAI 1966, BORSBOOM 1999, MEDAROV 2008). Values for VC, for example, are lowest around noon and highest between 3.00 and 4.00 pm (MEDAROV 2008), while DLco is highest between 08.00 and 09.00 am and decreases during the day (CINKOTAI 1966, MEDAROV 2008).

Introduction: The aim of this study was to investigate the diurnal rhythm for DLno. The DLno is a relatively new method and for applying in studies it is important to know whether there is a diurnal rhythm or not.

Methods: Eleven male subjects were measured between 8 am and 10 pm. In this period DLno was measured six times using a Masterscreen PFT-Pro (CareFusion), each time with a pause of at least two hours (max 4 hours).

Statistics: The Shapiro-Wilk test was used to test for normality. To determine diurnal variance, within-day variations were tested using the one-way Analysis of Variance (Anova). The Bonferroni correction was used for multiple comparisons. However, as diurnal variations can be curve shaped we also tested this index with a fractional polynomial regression model.

Results: The Anova test with Bonferroni correction showed no significant diurnal variation in DLno (p=0.854). Also the fractional polynomial regression model to the 4th degree or lower did not show any significant relationship between time of the day and DLno (p=0.526).

Conclusion: In our study DLno does not have a diurnal rhythm. We would like to expand our group of subjects to confirm this statement. Further investigation is therefore necessary.

P1218
Intra- and intersession variability of the single-breath determination of carbon monoxide diffusing capacity
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Background: Some lung function laboratories perform 3 instead of 2 reproducible tests for the single-breath determination of the carbon monoxide diffusing capacity (DLCO) with the underlying assumption that the average of 3 values is more reliable than the average of 2. Recent ATS/ERS guidelines (Eur Respir J 2005) established lung function device MasterScreen (Jaeger Ltd, Hohburg, Germany). Ten healthy subjects performed 2 tests on each device, whereas 24 patients performed only one measurement on the EOP as a part of their routine testing and we compared the results using t-tests with Bland & Altman analysis.

Results: The results (Table 1) show that the differences in TLCO, KCO and VAeff although statistically significant (p<0.05) were lower than the expected clinical repeatability. Analysis of patient and healthy subjects showed similar results. The between device variation was greater than the within Jaeger device variation.

Conclusion: The Easy One Pro gives values comparable with established gas transfer systems.

P1220
How long does it take for supine gas transfer to become stable after sitting up?
Liam O’Reilly, Helen Ward, Brendan Cooper. Lung Function & Sleep, Queen Elizabeth Hospital Birmingham, Birmingham, West Midlands, United Kingdom

Introduction: We are interested in using the change in gas transfer from sitting to supine in patients with various lung diseases, but were unable to find any published studies showing how long a subject should be supine before a stable representative measurement could be made. We looked at this in healthy subjects first.

Method: We measured single breath gas transfer (TLCO & KCO) using a MasterScreen lung function system (Jaeger Ltd, Hohburg, Germany) 3 times sitting at rest and then after approximately 10, 15, 20, 25 & 30 minutes respectively, lying supine in 14 healthy subjects (11F:3M; Ages: 22-51 years).

Results: The results (Table 1) show that TLCO and KCO increase by about 9% and 15% respectively and VAeff decreases by 5% from sitting to supine. Stability is reached after 15 minutes.

The determination of DLCO using 3 tests did not significantly reduce the within or between CV compared to the use of only 2 tests. Although adding the third test to estimate DLCO significantly reduced the value of DLCO (p<0.001), this reduction was not clinically relevant (~1% reduction in the value of DLCO). For the average healthy subject the DLCO varied as much as ±7% (2 tailed 95% confidence interval) during a 6 weeks period of time.

Conclusion: A DLCO determination based on 3 instead of 2 tests does not result in a more stable estimate of DLCO.

P1219
Comparison of two commercially available portable gas transfer devices
Lindsey Padddison, Maxine Jones, Brendan Cooper. Lung Function & Sleep, Queen Elizabeth Hospital Birmingham, Birmingham, West Midlands, United Kingdom

Introduction: We compared a novel portable gas transfer device which uses ultrasound and mass flow technology on healthy subjects and patients with suspected lung disease attending a routine lung function department.

Method: We measured single breath gas transfer (TLCO & KCO) on 34 subjects (20F:14M) using the EasyOnePro (EOP) (idd, Zurich, Switzerland) with an established lung function device MasterScreen (Jaeger Ltd, Hohburg, Germany). Ten healthy subjects performed 2 tests on each device, whereas 24 patients performed only one measurement on the EOP as a part of their routine testing and we compared the results using t-tests with Bland & Altman analysis.

Results: The results (Table 1) show that the differences in TLCO, KCO and VAeff although statistically significant (p<0.05) were lower than the expected clinical repeatability. Analysis of patient and healthy subjects showed similar results. The between device variation was greater than the within Jaeger device variation.

Discussion: This comparison of gas transfer measurement between the EOP and Jaeger systems shows that across a wide range of values the differences between the 2 devices are within the normal repeatability (S.I units) for TLCO, KCO and VAeff of <1.00, <0.50 and <0.20 respectively.

Conclusion: The Easy One Pro gives values comparable with established gas transfer systems.

Table 1. Gas transfer results

<table>
<thead>
<tr>
<th>Easy One Pro</th>
<th>Jaeger</th>
<th>EOP</th>
<th>Jaeger Mean Diff</th>
<th>Jaeger 1 – Jaeger 2 Mean Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLCO</td>
<td>6.43</td>
<td>6.03</td>
<td>0.40</td>
<td>0.15</td>
</tr>
<tr>
<td>KCO</td>
<td>1.36</td>
<td>1.29</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>VA</td>
<td>4.69</td>
<td>4.64</td>
<td>0.05</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 1. Lung function results

<table>
<thead>
<tr>
<th>Test</th>
<th>TLCO (liters/min/L)</th>
<th>KCO (liters/min/L)</th>
<th>VA (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy One Pro</td>
<td>6.43 (2.58)</td>
<td>1.36 (0.36)</td>
<td>4.69 (1.11)</td>
</tr>
<tr>
<td>Jaeger</td>
<td>6.03 (2.43)</td>
<td>1.29 (0.35)</td>
<td>4.64 (1.44)</td>
</tr>
</tbody>
</table>

Values shown as Mean (SD). TLCO in mmol/4L/min/L, KCO in mmol/4L/min/L, VA in L/min.

Discussion: We have shown that changes in gas transfer when supine stabilise after 15 minutes. Unexpectedly, not all subjects showed an increase gas transfer, with 6 showing no increase or a slight decrease when supine. This result needs further explanation.

Conclusion: Supine gas transfer should be measured after 15 minutes lying supine. Not all subjects produced an increase in gas transfer when supine.
115. Exercise tests and emerging outcomes: defining the impact of pulmonary rehabilitation

P1222
Effect of COPD severity on hemodynamic responses to exercise in patients with GOLD stages I-IV
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Introduction: Exercise-induced dynamic hyperinflation and large intrathoracic pressure swings can compromise the normal increase in cardiac output (Q) during exercise in COPD. Therefore, it is anticipated that the greater the disease severity, the greater would be the impairment in Q during exercise.

Aim: Thus, the aim of the study was to investigate whether the Q response is more severely impaired in the more advanced stages of COPD.

Method: We studied sixty COPD patients (15 patients at each stage, 1 to IV). Patients undertook a constant load test (75% Wmax) and a six minute walking test (6MWT). Q at rest and during exercise protocols measured by biochemical (PhysioFlow, Enduro) to determine the kinetic response at the onset of exercise (On-transient) and during recovery (Off-transient).

Results: While Q kinetics (On & Off) was not different between the two exercise protocols, on-transient and off-transient time constants were slower the more severe the disease severity was (Table 1).

Table 1. Q Kinetics (On & Off)

<table>
<thead>
<tr>
<th>GOLD Stages</th>
<th>On-transient Q (sec)</th>
<th>Off-transient Q (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT</td>
<td>Constant</td>
<td>6MWT</td>
</tr>
<tr>
<td>I</td>
<td>61.5±4.3s</td>
<td>43.9±1.6s</td>
</tr>
<tr>
<td>II</td>
<td>58.7±4.5s</td>
<td>64.7±2.8s</td>
</tr>
<tr>
<td>III</td>
<td>55.4±3.5s</td>
<td>69.3±3.5s</td>
</tr>
<tr>
<td>IV</td>
<td>105.7±4.5s</td>
<td>106.1±4.5s</td>
</tr>
</tbody>
</table>

Values are means ± SEM *Significant difference among stages.

Conclusion: The more advanced the disease severity the more impaired was the hemodynamic response to the 6MWT and the constant load test, possibly reflecting greater cardiovascular impairment in COPD or greater physical deconditioning. This study reflects, equally well as the constant load test, the degree of impairment in the hemodynamic response to exercise.

P1223
Electrocardiographic and echocardiographic abnormalities in COPD patients according to disease severity
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Epidemiological studies show high prevalence of cardiovascular disease (CVD) in COPD patients; however, few studies have assessed the prevalence of cardiac abnormalities in different stages of COPD. The aim of this study was to assess the prevalence of electrocardiographic and echocardiographic changes in 50 mild/very severe COPD patients (62% male gender, age= 67±9 years, FEV1= 56±23%). All individuals underwent to medical history and physical examination, electrocardiographic and Doppler echocardiography evaluations. Changes suggestive of ischemic heart disease occurred in 10% and mild left ventricular diastolic dysfunction in 88% independently of COPD stage. Mild/moderate COPD patients showed higher prevalence of anormalities in segmental contractility (p=0.01), while severe/very severe COPD patients showed higher prevalence of right ventricular overload (p=0.01) and increased right heart chambers (p=0.001). Age, male gender, systemic arterial blood pressure, C-reactive protein and BODE index were included in a multiple linear or logistic regression analysis with the left ventricular diastolic diameter/the size left atrium as dependent variables. Male gender and the BODE index were selected as predictors of left ventricular diastolic diameter/size left atrium as dependent variables. While Q kinetics (On-transient) and during recovery (Off-transient).

P1224
Effects of pulmonary rehabilitation (PR) on arterial stiffness in patients with COPD: The Brico study
Lowie Vanfleteren1, Martin Spruit2, Frans Franssen2, Martin Boorsma3, Jos Oep Rooij2, Miriam Groene3, Emiel Wouters1, 1Respiratory Medicine, Maastricht University Medical Center, Maastricht, Netherlands; 2Program Development Center, Ciro +, Centre of Expertise in Organ Failure, Horn, Netherlands; 3Research and Development, Astra Zeneca, Charnwood, United Kingdom

Background: Arterial stiffness, a strong predictor of cardiovascular mortality, is increased in patients with COPD. The effects of PR on arterial stiffness have been studied scarcely.

Methods: Pulmonary function, 6MWD, BML, SGRQ, mMSC dyspnea score, aortic pulse wave velocity (APWV), brachial pulse wave velocity (BPWV) and pulse wave analysis (SphygmoCor; AtCor Medical, Sydney, Australia) were determined in 102 patients (35 female; age: 64±7 years, FEV1= 53±17) with clinically stable COPD, prior and subsequently to a 35-session PR program including high-intensity interval and resistance training.

Results: 6MWD (+31,3 ±0.7, p<0.001), SGRQ (–2.4±1.8, p=0.001) and BMI (–0.5±1.1, p<0.001), and BMDP (+5.4±1.8 kg/m2, p=0.006) all improved, compared to baseline. Overall there were no changes in APWV, BPWV, central blood pressure and augmentation index (AI), while central and peripheral pulse pressure (PP) increased slightly. Peripheral PP increased by to a modest but significant reduction in peripheral diastolic blood pressure (DP). Also a significant, but clinically irrelevant reduction in heart rate (HR) was seen.

| Parameter | Baseline | After PR | P
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APWV, m/s</td>
<td>11.0±3.1</td>
<td>11.0±2.5</td>
<td>0.835</td>
</tr>
<tr>
<td>BPWV, m/s</td>
<td>8.9±2.1</td>
<td>8.8±2.1</td>
<td>0.997</td>
</tr>
<tr>
<td>SP, mmHg</td>
<td>137.9±20.9</td>
<td>137.7±21.1</td>
<td>0.868</td>
</tr>
<tr>
<td>DP, mmHg</td>
<td>82.3±6.4</td>
<td>80.8±6.6</td>
<td>0.034</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>54.0±16.1</td>
<td>57.4±15.3</td>
<td>0.017</td>
</tr>
<tr>
<td>Central SP, mmHg</td>
<td>127.2±9.6</td>
<td>128.9±11.8</td>
<td>0.270</td>
</tr>
<tr>
<td>Central DP, mmHg</td>
<td>82.3±6.4</td>
<td>80.8±6.6</td>
<td>0.176</td>
</tr>
<tr>
<td>Central PP, mmHg</td>
<td>45.2±14.5</td>
<td>47.8±14.7</td>
<td>0.026</td>
</tr>
<tr>
<td>Central AI (75 bpm)</td>
<td>20.6±8.8</td>
<td>29.2±8.3</td>
<td>0.457</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68.8±11.8</td>
<td>67.3±10.4</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Conclusion: On average, pulmonary rehabilitation does not reduce arterial stiffness in patients with COPD.
Reproducibility of a time trial cycle ergometer test protocol in comparison to a constant work rate test protocol in patients with COPD

Willem Gossens1,2, Josse Oomen1, Alex van Hyl1, Matthijs Hesseling2, Lars Berkhoudt1,2,3, Erik de Groot1,4,5,6, Lars Borghouts1,2, Willem Gosens1,2, Joost Oomen1, Alex van Hyl1, Matthijs Hesseling2, Lars Berkhoudt1,2,3, Erik de Groot1,4,5,6, Lars Borghouts1,2.

Introduction: In cardiopulmonary rehabilitation programs (CPR), constant-load cycle endurance tests (CLET) protocols are used to evaluate the response to specific interventions. In healthy subjects CLET protocols show a much lower reproducibility of the CLET protocol and TTT protocol on a cycle ergometer in patients with COPD.

Methods: In 20 patients with COPD (GOLD II-IV, FEV1 of 56.1±5.5% exercise performance was measured. Patients were randomly allocated to a CLET protocol or TTT protocol. Patients performed the test protocol to which they were assigned, five times. In the CLET group exercise to exhaustion at 120% of the actual individual training workload attained in the during CPR training sessions. Patients of the TTT group were asked to perform a certain amount of work (120% * Wstarting + 420) as fast as possible.

Results: CLET protocol showed a significantly lower coefficient of variation (CV) (6.5±1.6) than the TTT protocol (22.9±4.8) (p < 0.001). Individual CV (time to completion) ranged from 9.0% to 36.9% in the CWRT protocol and from 3.4% to 16.3% in the TTT protocol. There was a significant difference between the mean exercise time of the CLET (59.1±18.5 s) and the TTT (367±122 s) (p < 0.005). There were no differences in mean work (p = 0.058), power (p = 0.463), RPM (p = 0.629), subjective assessments of breathlessness (P = 0.55) and leg fatigue (P = 0.15) between the CLET and de TTT protocol.

Conclusions: The TTT protocol reproducibility was sign. higher than in the CLET protocol in patients with moderate-to-severe COPD.

P1227

Estimation of peak work load based on 6-min walk distance and general demographics in patients with COPD: A new regression equation


Background: Estimating peak work load to estimate Wpeak using 6-min walk distance (6MWD) are not accurate enough to target training intensity during pulmonary rehabilitation (PR) in patients with COPD (Sillen et al ERS 2011). We aimed to develop a new regression equation to estimate Wpeak using 6MWD and general demographics in COPD patients entering PR.

Methods: Measurements of lung function, body composition, and peak and functional exercise capacity were obtained in 3000 patients with COPD (53% men, age: 63.0±9.4 yrs; FEV1: 44.1±18% pred.), referred to 4 PR centres in the Netherlands (all member of the Vereniging Asmastra gegen Nederland). A stepwise multiple regression analysis was performed to estimate Wpeak using 6MWD, gender, age, height, body weight, fat free mass and FEV1.

Results: On average, patients had a normal body composition (BMI: 25.8±5.5 kg/m2, FFM: 16.9±18.4 kg, and a peak power (59±13 Watts) and functional exercise capacity (6MWD: 399±120 metres). The VAN regression equation derived from the stepwise multiple regression analysis was as follows: Wpeak = -52.787+(0.319*gender, women=0 and men=1)-(0.229*age in yrs)/(0.108*height in cm) + (0.267*body weight in kg) + (0.182*FFM in kg)/(0.132*6MWD in m)+(23.528* FEV1* in litres)

This regression equation explained 67% of the variation. The mean difference between the actual and the predicted Wpeak was 0.9±19 watts. 26% of the COPD patients had a predicted Wpeak which differed less than 5 watts (±5) of the actual Wpeak.

Conclusions: The level of accuracy of this newly derived regression equation seems too low to be used in individuals with COPD to target training intensity during PR.

P1228

Inhibitory effect of SABA on exercise dynamic lung hyperinflation during 6-min walk test in stable COPD patients

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Aim: The purpose of this study was to evaluate the inhibitory effect of short acting β2-receptor agonist (SABA) on exercise dynamic lung hyperinflation during the 6-minute walk test (6MWT) in stable COPD patients.

Subjects and methods: We examined 14 patients with stable COPD (mean age: 76yr, mean FEV1: 57.9% pred) who were referred to our clinic between July 2008 and October 2009. 6MWT and lung function test were performed after the inhalation of SABA (proteracol hydrochloride, 0.5 mg) or placebo. The Borg dyspnea score increased with time during 6MWT and was confirmed during every walk. There was no effect of day (p=0.23) on energy expenditure. There was no significant difference (0.0 [-0.4 to 0.3] METS) in energy expenditure between the actual and the predicted Wpeak.

Results: Compared to the baseline assessment, 6MWD increased by a mean of 20.5m when measured after inhalation of SABA (512.4±90.7m vs. 532.9±79.8m; p<0.05). During the 6MWT, inspiratory capacity (IC) decreased significantly with time. The IC after inhalation of SABA was significantly higher than the placebo. The Borg dysnea score increased with time during 6MWT and was attenuated significantly after inhalation SABA.

Conclusions: In the present study, there was a significant attenuation in exercise dynamic lung hyperinflation, suggesting the important rescue role SABA in the management of COPD. It is therefore likely that most patients with COPD may derive considerable benefit from rescue bronchodilator therapy with SABA.

P1229

Energy economy of walking with a wheeled ambulatory aid (rolloator) in patients with chronic obstructive pulmonary disease (COPD)

Kimberly Hill1, Thomas E. Dolmage2, Lynda Woon3, Tina Brooks1, Roger Goldstein1, 1School of Physiotherapy and Curtin Health Innovation Research Institute, Curtin University of Technology, Bentley, Western Australia, Australia; 2Respiratory Diagnostic & Evaluation Services, West Park Healthcare Centre, Toronto, ON, Canada; 3Department of Respiratory Medicine, West Park Healthcare Centre, Toronto, ON, Canada; 4Department of Physical Therapy, University of Toronto, Toronto, ON, Canada; 5Department of Respiratory Medicine, West Park Healthcare Centre, Toronto, ON, Canada.

Background: Probst et al. (Chest 126: 1102, 2004) reported that, when using a rolator, patients with COPD increased their distance walked in 6 min along with increased oxygen uptake and ventilation. It was difficult to appraise economy (mechanical work to total energy expenditure) because the main determinant of the energy demand, speed, varied between conditions; hence, the authors concluded that rolator use improved distance by increasing ventilatory capacity and/or economy.

Objective: To determine whether walking with a rolator improved the energy economy in patients with COPD. The hypothesis was that oxygen uptake, at the same speed, would be lower (improved economy) when walking with a rolator.

Methods: Subjects completed 2 walks, (with and without a rolator) at individually set and constant speeds. At least 24 h later they repeated the session for a total of 4 walks. Energy expenditure was estimated from measured oxygen uptake using a telemetric system. Since mechanical work was kept constant (speed) during each walk, differences in economy were reflected in differences in energy expenditure in metabolic equivalents (METS).

Results: Ten subjects completed the study. Attainment of a steady state was confirmed during every walk. There was no effect of day (p=0.23) on energy expenditure. There was no significant difference (0.0 (-0.4 to 0.3) METS) in energy expenditure with (3.6 [2.9 to 4.3] METS) or without (3.6 [2.9 to 4.3] METS) the rolator.
Conclusions: Rollator use does not acutely affect walking economy in patients with COPD. A better understanding of how people with COPD benefit from rollator use may facilitate their design and prescription.

P1232
Characterization of balance impairments in individuals with COPD
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Background: Balance deficits are increasingly recognized as an important secondary impairment in COPD, however little is known regarding the specific components of balance that are impaired.

Objectives: 1) To determine the specific components of postural control that are impaired in individuals with COPD compared to age-matched healthy controls; 2) To determine if deficits in balance in COPD are related to muscle strength or physical activity.

Methods: Balance, physical activity and lower extremity muscle strength were assessed in 37 patients with COPD and 20 healthy controls using the Balance Evaluation Systems Test (BESTest), the Physical Activity Scale for the Elderly (PASE), and an isokinetic dynamometer, respectively. A subset of subjects (20 COPD and 20 controls) underwent a second testing session in which postural perturbations were delivered using a lean-in-and-release system. Center of pressure data were collected from three force plates mounted in the platform.

Results: Subjects with COPD (age 71±7 yrs; FEV1 39±16 percent predicted) exhibited higher total, lower scores than controls (age 67±6 yrs) on all of the BESTest subscales (all p<0.001). The largest deteriorments in postural control were evident in biomechanics, transitions and gait. The PASE was a significant predictor of BESTest scores (p=0.034) in COPD. In response to anterior perturbations, subjects with COPD showed a longer time to foot-off (p=0.027) and foot-on (p=0.018) as well as a longer duration anticipatory phase (p=0.008) compared to controls.

Conclusions: Comprehensive balance assessment and management should be included in pulmonary rehabilitation. Deficits in balance in COPD appear to be related to decreased physical activity levels.

P1231
Comparison of maximal exercise capacity between patients with COPD from Brazil and United Kingdom
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Background: Field exercise tests such as the incremental shuttle walking test (ISWT) have been used worldwide in order to assess exercise capacity of patients with chronic obstructive pulmonary disease (COPD). However, the responses to this test in patients from different world regions have not yet been compared.

Objectives: To compare the responses to the ISWT between patients with COPD from Brazil and United Kingdom (UK).

Methods: 20 patients with COPD from Brazil were matched to 20 patients from the UK concerning gender distribution, age, body mass index and FEV1. All patients performed the ISWT during the baseline assessment for admission to a pulmonary rehabilitation program in their respective country. The total distance walked was recorded and heart rate (HR), oxygen saturation (SpO2) and dyspnea scores (Borg scale) were assessed before and after the test in both centers.

Results: In both groups, SpO2 decreased and HR and dyspnea scores increased significantly after the test (p<0.05 for all). Brazilian patients walked farther and achieved higher% of their maximal predicted HR than patients from the UK (345±173 vs 209±116 meters [p=0.006] and 80±12 vs 64±10%pred [p<0.001], respectively). The increase in dyspnea sensation after the test tended to be higher in the Brazilian group (4 [2-6] vs 2 [1-4], p=0.06).

Conclusions: Brazilian patients with COPD seem to walk more and achieve higher effort during the ISWT than patients from the United Kingdom. This is in line with previous data showing that patients from South America (especially Brazil) are more active in daily life and have better functional exercise capacity in comparison to patients from Europe and United States.

P1232
The effect of pulmonary rehabilitation on the sit-to-stand test in COPD
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Background: The sit-to-stand (STS) test is a component of the Short Physical Performance Battery (SPPB), it measures the fastest time to stand from a seated position 5 times with folded arms. We hypothesised the STS may be a useful outcome measure in COPD and that it would improve after an 8-week outpatient pulmonary rehabilitation (PR) program.

Methods: In 83 COPD patients (43M: 40F) referred to PR, the following were measured before and after PR: STS, incremental shuttle walk test (ISWT), MRC Dyspnea score (MRC) and St George’s Respiratory Questionnaire (SGRQ). Modified BODE (ISW as the exercise component) and ADO scores were calculated as composite mortality indices. Spearman’s rank correlation was used to assess the relationship between STS and ADO scores. The correlation coefficients and Wilcoxon signed rank test to assess the effect of PR on STS. We estimated minimal clinically important difference (MCID) using an anchor based approach against a 5-point Likert scale and the MCID of ISW.

Results: 18 patients were unable to complete STS either pre- or post-PR. 6 were unable to perform STS pre-PR but improved sufficiently to do so after PR. STS at baseline correlated significantly with ISW (r=0.53), MRC (r=0.35), modified BODE (r=0.26) and ADO (r=0.35), but not with age, FEV1, predicted, BMI or SGRQ. In 65 patients with full pre- and post-PR data, median STS time improved from 13.8s to 12.0s following PR (p<0.0001). Median improvement was -1.8s in those feeling “much better” after PR and -2.4s in those achieving the MCID of the ISW.

Conclusions: Not all COPD patients referred to PR can complete a STS. The STS is sensitive to change following PR. The MCID for the STS is probably of greater than 2 seconds.

P1233
Age of loss of walking ability in patients with Duchenne muscular dystrophy: A marker for the elective use of mechanical ventilation
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Introduction: In adolescence of Duchenne muscular dystrophy (DMD) comes the cardiorespiratory restrictive impairment (hypoventilation, sleep breathing disorder and order respiratory effort), marked by the loss of ambulation. At that time, the institution may be required ventilatory support. The onset of this reducing need for tracheostomy and increasing quality of life in DMD. Public Program (Ventilator-VIP) in John Paul II Child Hospital/Hospital Foundation of Minas Gerais State (IPIC/HPMFGS) assist DMD patients.

Objective: To evaluate loss of ambulation and the need to VS in patients with DMD in VIP/IPIC/HPMFGS.

Methods and patients: Cohort study, between 2002-2010 in VIP. Group A: 16 (25%) VS users and group B: 46 (74.2%) nonusers of VS. Likelihood of VS was estimated by survival analysis of Kaplan-Meier.

Results: Medians for the entire sample (years): last visit: 15.6 (4.0 to 30.2), monitored by the VP: 4.5 (0 to 6.5). Median age (years) loss of ambulation: A 8.1 (5.1-13), B 10.6 (7.15 to 15) (p=0.05). Majoritily in A lost early ambulation. Significant difference between the two groups (p=0.05). Survival curve of cumulative probability of VS: age < 11 years: no patient needed VS, 16 years: 20%, 23 years: 36%, and 26 years: 100%. Statistically significant difference in the cumulative probability (p<0.001) in need of SV among patients with loss of ambulation before 10 years (group C) and with loss of ambulation after that age (group D). 15 years of age, 12% of patients in C required SV. 100% needed to SV in C, in D only after 23 years.

Conclusions: Age of loss of ambulation at age 10 is a marker for estimating the need of early VS in patients with DMD.

P1234
In which male patients with COPD participated in a pulmonary rehabilitation program should be evaluated for osteoporosis? Dicle Kayraz1, Pinar Ergin2, Gülseren Kayalı3, Fatma Sengül4, Nese Demir2
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Osteoporosis is common in patients with COPD and an important risk factor for the development of hip, vertebral or long bone fracture which could add further disability and incapacity.

The aim of the study was to analyze the utility of different measures (age, smoking habit, daily dose of inhaled steroids, anthropometric measures of body composition, stage of COPD, dyspnea, health related quality of life, exercise capacity, comorbidities) for detecting the need for evaluation in male COPD patients who were participated in a PR programme.

Methods: Patients who were in a pulmonary rehabilitation programme with confirmed stable COPD and not on long-term oral corticosteroids (n=57) performed spirometry. They underwent nutritional assessment by midarm circumference,calculation BMI and FFMI. Dyspnea sensation was assessed with the MRC, where health related quality of life was assessed with the SGRQ,Exercise capacity was measured using the SWT.All had DXA assessment of Bone Mineral Density.
**Results:** A total of 57 COPD patients with the mean age of 62.07±7.7 years. Osteoporosis was found in 22 patients (38.6%) at both the total hip and total lumbar spine. After adjusting for all covariates (age, FEV1, daily dose of inhaled steroids and smoking pack years) COPD patients with a lower BMI was found to be at an increased risk of hip region osteoporosis. The adjusted odds ratio for BMI 0.51 (0.28-0.91), P=0.023.

The addition any of the other measurements was not found as a risk factor for osteoporosis. Comorbid nutritional assessment, incorporating a calculation of their BMI may confer benefit detecting those at risk of osteoporosis in male COPD patients.

**P1235**

The effectiveness of pulmonary rehabilitation in COPD outpatients with comorbidities
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**Aim:** Chronic obstructive pulmonary disease (COPD) is often associated with other chronic diseases. The aim of this study was to determine the frequency and prevalence of chronic comorbidities in patients with COPD and to assess their influence on the effects of pulmonary rehabilitation (PR).

**Method:** 183 patients were included multidisciplinary comprehensive PR program between July 2007 and September 2010 in our outpatient PR center. All patients were grouped according to the following comorbidity categories: 0 (absence of comorbidity), 1 and >2 (depending on the number of comorbidity). Incremental Shuttle Walking Test (ISWT) and Endurance Shuttle Walking Test (ESWT) was used to evaluate exercise capacity. Medical Research Council (MRC) for the perception of dyspnea, St. George’s Respiratory Questionnaire (SGRQ) for quality of life, Hospital Anxiety and Depression Scale (HADS) for psychological evaluation and BMI, fat-free mass (FFM), fat-free mass index (FFMI) analyzing for body composition.

**Results:** 131 patients reported at least one chronic comorbidity added to COPD. Metabolic (systemic hypertension, diabetes, dyslipidemia) and heart diseases (chronic heart failure, coronary heart disease) were the most frequently reported comorbid combinations (88 and 23, respectively).Statistically significant improvement was determined in ISWT and ESWT (p<0.01); statistically significant decrease was determined in MRC, SGRQ and HADS (p<0.001) for each comorbid categories.

**Conclusion:** Chronic comorbidities are very frequent in patients with COPD undergoing PR. Comorbidities does not preclude access to effectiveness of rehabilitation.

**P1236**

Comorbidities in COPD patients are not associated to higher disease severity
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The influence of disease severity on the prevalence of comorbidities in COPD patients is unclear. The aim of this study was to assess the prevalence of comorbidities in 25 mild/moderate COPD patients (68% male gender, age=65±8 years, FEV1=73±15%predicted) and 25 severe/very severity COPD patients (56% male gender, age=69±9 years, FEV1=40±18%). Comorbidities were registered based on medical charts diagnoses, on Charlson comorbidity index and on Hospital Anxiety and Depression Scale. Of the 50 patients evaluated, 70% had diagnosis of comorbidities, and 42% of these were cardiovascular diseases (40% hypertension, 10% coronary artery disease and 6% heart failure grade I). Depression was present in 20% of patients, dyslipidemia in 14% and diabetes mellitus in 14%. The prevalence of dyslipidemia (p=0.02), depression (0.008) and alcoholism (p=0.06) were higher in patients with mild to moderate disease. Charlson comorbidity index, systemic arterial blood pressure, diabetes mellitus, ischemic heart disease and chronic cardiac failure and the scores of the Hospital Anxiety and Depression Scale were similar between both groups. The majority of patients with diagnostic of dyslipidemia had concentrations of lipids (total cholesterol, HDL, LDL and triglycerides) within normal values and the lipid profile were similar between groups. In conclusion, comorbidities are highly prevalent in COPD patients regardless of the disease severity. Some diseases such as dyslipidemia, depression and alcoholism are even more prevalent in mild/moderate patients.

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**116. Exacerbations and severe chronic respiratory disease: oxygen, rehabilitation, admission to hospital and palliative care**

**P1237**

Late-breaking abstract: Effects of mucus clearance on the differences of rheological property, driving pressure and frequency during high frequency chest wall oscillation (HF CWV)
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**Background:** HF CWO is commonly used for airway clearance. However the effect of mucus clearance on the rheological property, driving pressure and frequency during HF CWO is not clear. The purpose of this study is to clarify differences of airway clearance efficacy.

**Method:** 24 normal subjects participated in the study 1. Mucus stimulants (MS) were prepared using thicker 1, 2, 3 and 4% and the pressure controls of SmartVest™ were driven 20, 40 and 60 on the frequency 13Hz. MS rheological studied were measured using Rheometer. They were quiet breathing into the endotracheal tubes having internal diameter of 7mm during SmartVest™. We measured migration velocity of each MS, PEFR, Pmax and effortless breathing. Another 26 normal subjects participated in the study 2. MS were prepared using similar thicker were driven frequency 9Hz, 13Hz and 17Hz on the driving pressure 40.

**Measurement methods and items were carried out in a similar manner of Study 1.**

**Results:** The higher setting pressure and frequency controls drove, the more PEFR and Pmax increased (p<0.05). In the rheology of MS, the lower viscoelasticity of 1% MS had, the faster clearance velocity moved (p<0.05). However, the clearance velocity did not increase in the higher viscoelasticity of MS in spite of high driving pressure. The 13Hz oscillation was most reduced in viscoelasticity and yield value by comparison with 9Hz and 17Hz. The lower viscoelasticity of MS in the each frequency, the clearance velocity increased (p<0.05). The subjects were not tolerable on17Hz.

**Conclusions:** The oscillation of 13Hz and driving pressure 40 is the most effective for mucus clearance.

**P1238**

Assessment of nocturnal hypoventilation in patients with chronic respiratory failure: Role of transcutaneous PCO2 monitoring. An observational study
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Patients with nocturnal hypoventilation are at risk of developing daytime ventilatory failure. As a result, this finding has therapeutic implications. Currently, assessment of nocturnal hypoventilation is performed using nocturnal oximetry (NO) coupled to diurnal arterial blood gases (ABG). Even if theoretically useful, transcutaneous PCO2 (TcPCO2) monitoring is not routinely used. Therefore, its role should be defined.

**Objectives:** To compare NO coupled to ABG versus TcPCO2 for detecting alveolar hypoventilation in a cohort of chronic respiratory failure patients.

**Methods:** We performed 153 NO coupled to a TcPCO2 recording (91 under non invasive ventilation and 62 during spontaneous breathing) in 98 patients. In addition, ABG were performed during spontaneous breathing. Aetiologies of respiratory failure were: neuromuscular disorder (97 traces), thoracic cage abnormalities (35 traces) and lung disease (21 traces). Nocturnal hypercapnia was defined by a nighttime mean PaCO2 ≥ 50 mmHg, nocturnal hypoxemia as ≥ 30% of the night spent with a SaO2 <90% and diurnal hypercapnia as a PaCO2 ≥45 mmHg.

**Results:** Combined normal NO and normal ABG underestimated nocturnal hypercapnia in >50% of both spontaneously breathing and ventilated patients. Conversely, nocturnal hypoxemia was associated with nocturnal hypoventilation in 100% of non ventilated patients but only in 50% of ventilated ones.

**Conclusion:** Normal values of nocturnal oximetry and/or ABG do not allow to exclude nocturnal hypoventilation. Our results underline the interest of performing transcutaneous TcPCO2 monitoring to evaluate patients at risk of nocturnal hypoventilation.
P1239
Evaluation of home oxygen provision in east London: A study of appropriateness of ordering, and patient understanding and compliance
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Introduction: In the UK, commissioners fund home oxygen via a tariff based on flow rates, hours of prescribed usage, and mode of delivery; each specified on an oxygen order form (HOOF).
Aims: Over six months, records from the local supplier (Air Products) showed 130 patients were under-using oxygen by at least 75% of that ordered. This study aimed to evaluate why.
Methods: Diagnoses and reasons for oxygen provision were obtained from electronic records. Patients were telephoned to explore understanding of the need for oxygen, health benefits, and their individual order. Some were deceased (11), were children, or were not contactable. Data on contactable adults, who agreed to interview (45), are presented.
Results: Commonest reasons for oxygen provision were COPD and obesity hypoventilation/obstructive sleep apnoea. 47% (21/45) could not name their oxygen.

Conclusions: This study confirms the hypothesis that a LTOT “complex” service, may have greater effectiveness than a “complex”, in reducing the exacerbations rate, the number and the length of the hospitalizations of the COPD patients.

P1241
End of life in COPD: There may be no surprises!
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Background: In the UK prognostic indicators have been developed for predicting end of life (EOL) in COPD.
We report on the prevalence of these indicators in patients admitted to a nurse led unit for people with acute exacerbations of COPD (AE-COPD).
Methods: Data on general and COPD specific prognostic indicators plus the surprise question were collected on all admissions Aug 2010 to Jan 2011.
Results: Total 199 patients (54/4%). Mean age 70 (37-93). In 86 (48%) cases the clinician would not have been surprised if the patient died in the next 6-12 months. In only 5 of these instances were no other prognostic indicators identified (positive predictive value of negative response 95%) 174 (87%) had at least 1 prognostic indicator identified at the time of admission.

Prognostic indicators and surprise question

<table>
<thead>
<tr>
<th>Prognostic Indicator</th>
<th>Surprise Q “No” (n=96)</th>
<th>Surprise Q “Yes” (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidities (BEDHF/EDM)</td>
<td>45 (47)</td>
<td>43 (42)</td>
</tr>
<tr>
<td>NY/Loss &gt; 10% over 6 months</td>
<td>9 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>BMI &lt; 19</td>
<td>17 (18)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Anemia &lt; 25 g/dl</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kaminsky &lt; 50</td>
<td>9 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>&gt; 3 admissions in 12 mths</td>
<td>35 (37)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>LTOT</td>
<td>24 (25)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>MRC 5</td>
<td>44 (46)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>FEV1 &lt; 50% pred</td>
<td>33 (34)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Right Heart Failure</td>
<td>13 (14)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>NIV/ICU</td>
<td>28 (29)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Sputum MRSA or Pseudomonas</td>
<td>12 (13)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>&gt; 3 courses of steroids in 12 mths</td>
<td>19 (20)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>HAD Depression &gt; 11</td>
<td>26 (27)</td>
<td>23 (23)</td>
</tr>
</tbody>
</table>

Of the 15 deaths so far there was a negative response to the surprise question in 14 and in all at least 1 other prognostic indicator was present.
Conclusions: Prognostic indicators were present in 87% of patients admitted.
The surprise question should form part of admission assessment.
It is too early to say which prognostic indicators are important in predicting EOL.

P1242
Are COPD patients referred to palliative care?
Respiratory Medicine, Basildon & Thurrock University Hospital, Basildon, United Kingdom

Introduction: The consultation on a strategy for COPD in England suggests patients with COPD should be considered for end of life care particularly if they have the following markers of severity: 1. Severe airflow obstruction (FEV1 <30%) 2. Low BMI (<20) 3. Housebound 4. Two or more admissions in previous year 5. Respiratory failure or previous ventilation.
Method: A list of patients discharged in Jan 2007 with a diagnosis of COPD was obtained. Of 69 patients identified 40 were chosen at random and included. The case notes were investigated and the markers of severity met were recorded. It was also determined if the patients had survived to discharge, 3 months and 3 years.

Results:

<table>
<thead>
<tr>
<th>No. of markers of severity met</th>
<th>Patients Died during admission</th>
<th>Survived to discharge</th>
<th>Alive at 3 months</th>
<th>Alive at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>3 (5%)</td>
<td>11 (92%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>4 (40%)</td>
<td>6 (60%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>5 (55%)</td>
<td>4 (44%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion: None of the patients had all 5 criteria measured during, or prior to the admission in question illustrating the importance of thoroughly assessing level of disability in COPD. When considering the patients alive at 3 years there was a trend towards fewer patients surviving the greater the number of severity criteria they met. However the patient who met 4 of the severity criteria, and survived to 3 years demonstrates the difficulty in precisely predicting the transition to the end of life in COPD and thus timing of involvement of palliative care. Only 3 of the 40 patients were considered for specialist palliative care, and this consisted of using
the Liverpool care pathway in the hours prior to death. More studies are needed to look into optimal timing for end of life care in COPD.

P1243

Readmission predictors in patients with chronic obstructive pulmonary disease due to an exacerbation

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Introduction: Hospitalizations for chronic obstructive pulmonary disease (COPD) exacerbations increase risk of readmission due to an exacerbation and lead to higher mortality.

Aims: To determine factors which may contribute to readmission due to a new episode of COPD exacerbation.

Methods: We reviewed medical charts of all patients with a discharge diagnosis of a COPD exacerbation admitted to Fukuyagi hospital, the secondary respiratory hospital serving the north-west of Tokyo, from October 2008 to March 2010. Data collected included age, sex, pack-year history of smoking, body mass index (BMI), previous FEV1, arterial blood gases at an emergency room, and incidence of long term oxygen therapy (LTOT). Comorbidities were measured with Charlson Comorbidity Index. Length of stay at this time as well as the number of hospitalizations for a COPD exacerbation in the previous 12 months were obtained. Readmission was defined as one or more hospitalization for an exacerbation within six months after discharge.

Results: 57 patients (57 men) were included in this study (mean FEV1 38.4% predicted). 19 of these patients (28.8%) were readmitted. Readmission was significantly associated with receiving LTOT (odds ratio [OR], 3.63 [95%CI, 1.18 to 11.2], p=0.04), hospitalizations for a COPD exacerbation in the previous 12 months (OR, 20.2 [CI, 4.58 to 88.1], p<0.001), and Charlson Comorbidity Index (≥1 vs 0 or 1) (OR, 7.56 [CI, 2.08 to 27.53], p=0.003).

Conclusions: Receiving LTOT, hospitalizations during the previous year, and comorbidities are strong predictors of readmission due to a new episode of exacerbation in our COPD patients.

P1244

A time-limited, six month program of community-based disease management, support and education following hospital admission for A/E COPD; outcomes from a pilot study

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Introduction: Our specialist multidisciplinary respiratory team (MDRT) can successfully support COPD patients following A/E COPD admission (>1000 bed-days saved/year). Patient-dependency has made discharge difficult. The aim of this pilot study was to determine the efficacy/suitability of a time-limited (6/12) support program, focused on self-management.

Method: Patients admitted with A/E COPD ≥2/year or with first time with no previous diagnosis/education, were referred. Disease severity, anxiety/depression and admission frequency (year before/year after) were documented. A pre-determined program of self-management skills was assessed by the Bristol QoL (BQ).

Results: 23 COPD patients, mean (±SD) age 73.3±3.02 years; FEV1 0.79±0.07; MRCDS 4.1±1.0 were included in this pilot study for 6.4±0.9 months (mean±SE). 11/23 were discharged appropriately; 2 died; 23 required ongoing support. There was no significant difference in disease severity or HADS between those discharged and those requiring ongoing support. Admission rate significantly (p<0.02) decreased from 1.9±0.2/patient in 12/12 prior to MDRT to 1.2±0.3/patient in 12/12 after team input, in both groups with no significant difference in final BQ (39.3±3.9 vs 44.0±4.4) scores.

Conclusion: A time-limited program focused on self-management is appropriate for about 50% patients admitted with severe COPD. Further work needs to be done to determine specific factors that can predict which patients are suitable for this intervention.

P1245

Evaluation of contribution of high frequency chest wall oscillation treatment to medical treatment in patients with acute exacerbations of COPD

Tugba Goktalay, Selin Akbas, Fatma Yagci, Aysu Demir, Mert Eryilmaz, Kilis, Turkey

Vest TM device which applies high frequency chest wall oscillation has been approved by FDA for the clearance of bronchial secretions in 1988 and for the induction of sputum in 2000. It has been used in abroad but not in Turkey yet. The Vest TM device was applied to 16 of 30 patients. Basal BODE index of the study groups was not statistically different, also mean age was similar BODE index, PO2 and SO2 of the patients were statistically better both on the third and fifth days (Table). There was a 4% increase from basal FEV1 of Group1, while this difference was 6% in Group2 (p<0.002, p=0.002). Similarly the increase in 6MWT was 107m in Group 1 while it was 150m in VestTM group (p=0.000, p=0.000). Although MMRC dyspnea scale did not statistically different, the VestTM group reported decreased dyspnea perception (p<0.055) BODE index (p=0.801), p=0.595 and SpO2 (p=0.640, p=0.870) were not found different between the two groups.

Adding Vest TM to conventional treatment in COPD exacerbations did not result in any difference in BODE index, however exercise capacity and dyspnea perception were found to be improved more with Vest TM.

P1246

Hospital at home for patients with acute exacerbations of chronic obstructive pulmonary disease; will it be an effective home care model?

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The current acute care model for COPD is, in general, insufficient for optimal management of the disease. Coordination of services is especially important at the time of the COPD exacerbation, which is characterised by high morbidity, high healthcare utilisation and even worse fragmentation of care. Home care services can offer a great potential for this aim, Hospital at home (HAH) care model is feasible, simple, and efficacious for certain patients with selected acute medical illnesses who require acute hospital-level care.

Aim: The aim of the present study was to analyze the effectiveness of HAH for patients with COPD exacerbation.

Methods: Two hundred and six patients who were admitted to our institution via the emergency department with the diagnosis of COPD exacerbation were included to HAH. Patients were followed up during the year after HAH practise.

Hospitalization rates, emergency department, home admnistration days, hospitalisation days when needed were evaluated before and after one year period of HAH

Results: After one year follow up period of HAH practise hospitalisation rates, emergency department and out patient clinic admnitions, length of hospital stay were decreased. Respectively 40.29% 21.84% and 46.35%. The decreases for all parameters were found statistical significant (p<0.01).

Conclusion: We conclude that integrated care services including home care using the HAH modalities are strongly needed to enhance both health and managerial outcomes. Clinicians should consider this form of management, especially as there is increasing pressure for inpatient beds in Turkey.

P1247

Hand grip strength in patients engaged in pulmonary rehabilitation program during COPD exacerbation

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Aims: To measure hand grip strengths and investigate related factors in COPD patients engaged in pulmonary rehabilitation program during exacerbation.

Material and methods: Grip strengths of both hands were measured using viconometry in 52 COPD patients.

Results: Mean hand grip strength were 0.41±0.14 bar. Patients were divided into two groups according to a cut-off point, 0.40 bar (54% ≤ 0.40, 46% >0.40), there was no significant difference in age, systemic diseases, FEV1/FVC, arterial blood gases between groups. Hand grip strengths were lower in women (p=0.003). In patients with lower strength, FEV1, FVC values (p=0.019 and p=0.002, respectively), hemoglobin levels, mini-nutritional scores and T scores at femoral neck were lower than that of patients with higher strength (p<0.05). The difference in 6 minute walk distance was not significant (p=0.087). However patients in the lower strength group had higher fatigue levels (p=0.039) and higher rest number during the walk test (p=0.032).

There was a moderate positive correlation between grip strength and 6-minute walk distance (r=0.511, p=0.001). There were negative correlations between strength and test duration and number (r=-0.339, p=0.03 and r=-0.664, p=0.002), saturation changes (r=-0.383, p=0.012), dyspnea and fatigue levels (r=-0.475, p=0.001) during the walk test.

Conclusion: Hand grip strengths of COPD patients in exacerbation showed good correlation with 6-minute walk test, indicator of functional capacity. Hand grip strength measurement which is simple to perform and has low cost may be a helpful indicator of muscle performance, especially when 6-minute walk test can be performed during exacerbation.
Effects of case management on hospitalisation and exacerbation rate in severe, complex COPD: A randomized controlled trial

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Background: Acute exacerbations have negative effects on lung function, physical performance, dyspnoea, and quality of life. Patients with severe COPD and co-morbidities are especially vulnerable to exacerbations.

Aim: We investigated if a case manager could reduce number and duration of hospital admissions due to exacerbations of COPD.

Method: In this RCT, 81 COPD patients GOLD stage 3–4 and co-morbid disease, with ≥1 reported exacerbation in the past 2 years were randomised to usual care or a case management care condition. In the usual care condition, patients visited the pulmonary nurse every 3 to 6 months. In the case manager condition, the pulmonary nurse started with a home visit, and contacted patients at least every 6 weeks by phone. Basic self-management techniques were taught and an exacerbation action plan was offered to the patient and all health care providers.

Results: Number and duration of hospital admissions were not lower in the experimental condition. The number of exacerbations reported by the general practitioner did not differ significantly. No differences were found between the two conditions with respect to health status measured by the CRQ. There was major drop out in both groups (42%), main reason was death (53%). Patients were more satisfied with the experimental condition, particularly because the case manager helped coordinating the complex care by many professionals.

Conclusions: Benefits on health status and hospital admission rates and duration were not found. However, patients with severe COPD and multiple co-morbidities benefit from a case manager by structuring care in a better way leading to increased patient satisfaction.

P249 The current situation and the perspective of respiratory care in Japanese COPD patients revealed by Japanese White Paper on home respiratory care 2010 – COPD subgroup analysis

Jun Ueda1, Michiaki Mishima2, Koichiro Tatsunami3, Kazunisha Takahashi3, Hideki Ishihara4, Hajime Kuroswa4, Keisaku Fujimoto5, Mariko Koyama6, Kazuko Toyama7, 8, 9, 10 Clinical Research Unit of Internal Medicine, School of Health Care and Nursing, Urayasu, Japan; 2Department of Respiratory Medicine, Graduate School of Medicine, University of Tokyo, Japan; 3Department of Primary and Community Care, Urayasu, Japan; 4The Japan Respiratory Society; 5Department of Respiratory Medicine, Tokyo Medical College, Tokyo, Japan; 6The Japan Federation of Pulmonary Rehabilitation Working Group, Tokyo, Japan; 7Department of Primary Care and Nursing, Urayasu, Japan; 8Department of Respiratory Medicine, Tokyo Medical College, Tokyo, Japan; 9Respiratory Care Committee, The Japan Respiratory Society, Tokyo, Japan; 10Committee, The Japan Respiratory Society, Tokyo, Japan

To assess the current situation and the perspective of respiratory care of outpatients with chronic respiratory diseases, the nationwide survey was conducted. In the patient survey, the questionnaires were sent to 3090 patients (JFPPORD) and the return rate was 27%. Of the 338 COPD patients, 73% were receiving LTOT (LTOT and HMV 24%). With regard to the pharmacological treatment, Tiotropium, LABAs, ICXs, mucolytic agents, macrolides were prescribed in 57%, 72%, 50%, 51%, and 20%, respectively. Those receiving pulmonary rehabilitation (PR) and nutritional guidance accounted for 65% and 42%, which was 60% and 28% in the 2002 White Paper respectively. Among the LTOT/HMV group, 31% had been hospitalized more than once in the past year due to exacerbation. Concerning wishes for medical staffs, the most common reply was they wanted to be taught more about the skills for self-management, which were 78% and 83% in 2010 and 2005, respectively. The most common concrete examples of this concerned PR. The three most common demands concerning LTOT were a wish for subsidy of electricity cost of the concentrator (45%), for distribution or rental of oximeters (41%), and better explanation of the response of the LTOT/HMV providers in the time of natural disaster (35%). It is suggested that there are demands regarding the needs of patients for more information about the self-management skills and an increase in opportunity to receive PR. To achieve anxiety-free respiratory care for handling of patients in the time of natural disaster. To consider the skills for self-management, which were 78% and 83% in 2010 and 2005, respectively. The most common concrete examples of this concerned PR. The three most common demands concerning LTOT were a wish for subsidy of electricity cost of the concentrator (45%), for distribution or rental of oximeters (41%), and better explanation of the response of the LTOT/HMV providers in the time of natural disaster (35%). It is suggested that there are demands regarding the needs of patients for more information about the self-management skills and an increase in opportunity to receive PR. To achieve anxiety-free respiratory care for handling of patients in the time of natural disaster.

P250 The "susceptibility to exacerbation" phenotype in COPD and response to pulmonary rehabilitation

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Introduction: Exacerbations are a key feature of COPD and are known to impact lung function, daily physical activity level, quality of life, survival, and health resource usage. Pulmonary rehabilitation (PR) is an effective treatment for disability in COPD, with previous research identifying improved outcomes for patients reporting no exacerbations (NE) when compared with patients suffering exacerbations (NE) (Rioardo-Sforza et al., 2005). A frequent susceptibility exacerbation phenotype (≥2 exacerbations in previous year) has been identified (Hurst et al., 2010) which may have implications for response to PR. We hypothesised that patients with frequent exacerbations (FE) would gain less benefit from an 8-week outpatient PR program.

Method: In 93 COPD patients reporting NE (n=28), one exacerbation (OE) (n=28) or FE (n=37) in the previous year, the following assessments were made before (T0) and after (T1) PR: fat free mass (FFM), incremental shuttle walk (ISW), self-report Chronic Respiratory Disease Questionnaire (CRQ-DQ-SR).Median(IQR) change in ISW, FFM, and CRQ-DQ-SR total score from T0 to T1 was compared between groups using Kruskal-Wallis tests.

Results: ISW distance and CRQ-DQ increased in NE (80 (13-148) m, 13.5 (1.5-23.8) OE (50 (0-110) m, 19.0 (2.0-32.0)) and FE (60 (20-270) m, 21.0 (8.0-28.0)) groups.FFM increased in NE (0.36 (-1.32-1.20)) kg) and OE (0.51 (0.85-1.33) kg) but not FE (0.07 (-1.38-2.99) kg).No significant differences were found between groups for any variables (ISW: p = 0.46, CRQ-DQ total p = 0.35, FFM: p = 0.94).

Conclusion: The "susceptibility to exacerbation" phenotype does not appear to affect improvements in exercise capacity, or health related quality of life gained during PR.

P251 Promoting excellence in COAD care – Through a community multidisciplinary team approach

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Background: It was estimated that the prevalence of COPD among the elderly Chinese living in Hong Kong was 25.9%.

Method: The COAD Alliance Community Program was designed and carried out by a community hospital in Hong Kong. It involves a multidisciplinary team of specialists via a community outreach approach. The highly dedicated team includes respiratory physicians, physiotherapists, occupational therapists, community outreach nurses, and others. High risk COPD patients with more than 3 emergency room or hospital admissions per year were invited and recruited into the program. They were then assessed by case manager who were responsible organizing the community based services for these patients. Services provided include advice and information provision, self care management at home, outreach nursing visits, outpatient physiotherapy sessions and emotional/counseling support. These patients’ “pre – program” and “post – program” emergency room admission rates, inpatient admissions and hospital inpatient bed-days were recorded and tabulated.

Results: 100 patients were recruited into the COAD Alliance Community Program. Six patients died during the study and 12 patients remaining for analysis. Reduction in AED attendance (mean number of admission of 2.38 pre program c.f 1.68 post program) and medical ward admissions (1.6 c.f 0.85) was evident. There is also a significant reduction in hospital inpatient bed-days (8.16 pre program c.f 4.42 days post program, p = 0.05). Total cost reduction is 215,028 Euros.

Conclusion: The multidisciplinary approach was effective in reducing emergency room attendances, inpatient bed–days and total health expenditure.

P252 Breathlessness and social cognition: The effect of social comparison on perceived breathlessness in asthma and COPD

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Aim: The effect of context variables on the perception of breathlessness has been investigated extensively, but not in a social cognitive framework. Our aim was to test how findings in social cognition can be translated from general self-perception to research on dyspnea. We investigated the effect of social comparison on perceived dyspnea in an experimental study in asthma patients and in a field study in COPD patients in rehabilitation.

Methods: In Study 1, 50 asthma patients participated in an experiment with two sequences of resistive load breathing. Both sequences were preceded by the presentation of one of two social comparison standards. We measured reported dyspnea and persistence in load breathing. In Study 2, 48 patients with COPD completed measures on social comparison at the start and end of rehabilitation as well as on perceived dyspnea during activity. In both studies, we expected comparison standards to affect self-report of breathlessness. We controlled for functional parameters such as lung function (Study 1) and BODE index (Study 2).

Results: In both studies, we found an significant impact of social comparison on the report of breathlessness. In Study 1, we found social comparison to have an impact on persistence in load breathing. Furthermore, as moderator of the relationship of social comparison and dyspnea we identified perceived similarity with comparison standard.

Conclusion: Social cognitive processes can shape the perception of breathlessness. Particularly in settings with a strong social component such as group exercise training in rehabilitation, these social cognitive mechanisms might be important targets to improve exercise persistence.
P1253
Participants perspectives of living with COPD: The role of different groups of health professionals
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Methodology: This is a qualitative research study of participants experiences of a pulmonary rehabilitation (PR) programme based in Wakefield, UK. 4 group interviews were carried out in spring 2010 involving 24 participants. 22 had a primary diagnosis of COPD (mean FEV1 1.1 litres, 42% predicted), 1 had lung cancer and 1 was a carer for a participant with COPD. A structured interview included discussion of the roles of different groups of health professionals - general practitioners (GP) and nurse specialists.

Results: Participants liked their GP to have good communication skills. Specific examples of good practice were describing illness in a manner which the participant could understand and allowing time to ask questions. Participants appreciated the amount of time they were able to spend with a doctor, liked regular contact with the same GP and the cleared waiting for appointments. Participants wanted to feel that something could be done to improve their situation, trusted doctors decision making and rarely asked questions regarding their treatments. Specialist nurses were considered to be more helpful in managing symptoms than GPs. Nurses had more time for patients, were more likely to involve patients in decision making, and showed greater empathy. Some nursing staff were considered to have more specialist knowledge than GPs. Participants described a high degree of trust in nurses decision making and were more comfortable discussing their condition with them.

Summary: Patients with COPD value good communication skills, expert knowledge, a positive approach and good time management in their health providers. Specialist nurses are able to deliver an effective patient-centred service.

P1254
The impact of depression in recovery and outcome of patients hospitalized for COPD exacerbation
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Background: Depression has been associated with worsening of COPD symptoms and quality of life, more exacerbations and increased mortality.

Objectives: To evaluate prospectively the impact of depressive symptoms on patients with COPD exacerbation.

Methods: Twenty-one patients (VEF1: 46±10% predicted) were evaluated monthly for one year.

Results: Depression was diagnosed in 7 patients (33.3%) and a depressive symptom was present in 7 patients (33.3%). There was a significant reduction in MVIC after IET was observed just for MD at moments 10, 30, 60 minutes and it was recovered in 24h.

Conclusion: Muscle weakness and a susceptibility to develop muscle fatigue after walking occur in the patient and dorsi-flexor muscles in patients with COPD compared to controls.

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P1256
Upper and lower limbs muscle in patients with COPD: Similar muscle efficiency but differences in resistance to fatigue
Eduardo Foschini Miranda, Carla Malaguti, Paolo Marchetti, Simone Dal Corso. Rehabilitation Sciences, Nove di Julia University, São Paulo, Brazil

Background: It is still controversy whether the impairment of muscle function is homogeneous between the upper and lower limbs in patients with COPD.

Objective: To compare muscle function between quadriceps femoris (QF) and middle deltoid (MD) after a fatigue protocol and also the recovery time fatigue.

Methods: Twenty-one patients (VEF1: 46±10% predicted) performed for both muscles: maximum voluntary isometric contraction (MVIC) and post-exercise for either plantar-flexor (P1257) or dorsi-flexor muscles.

Conclusion: Muscle weakness and a susceptibility to develop muscle fatigue after walking occur in the patient and dorsi-flexor muscles in patients with COPD compared to controls.

P1257
How should we measure arm exercise capacity in COPD? A systematic review
Tanya Janaudis-Ferreira1,2, Marla K. Beauchamp3, Roger S. Goldstein1,2, Dina Brooks1,2. 1Respiratory Medicine, West Park Healthcare Centre, Toronto, ON, Canada; 2Department of Physical Therapy, University of Toronto, Toronto, Canada; 3Department of Medicine, University of Toronto, Toronto, Canada

Background: There are no recommendations on how to measure arm exercise capacity in individuals with chronic obstructive pulmonary disease (COPD). The objectives of this study were to: (i) synthesize the literature on measures of arm exercise capacity in individuals with COPD; (ii) describe the psychometric properties and the target construct of each measure and (iii) make recommendations for clinical practice and research.

Methods: Studies conducted in COPD that included a measure of arm exercise capacity were identified after searches of 5 electronic databases (MEDLINE, CINAHL, EMBASE, Physiotherapy Evidence Database and Cochrane Library) and reference lists of pertinent articles. One reviewer performed data extraction and two assessed quality of studies that described measurement properties using the Consensus-based standards for the selection of health measurement instrument.

Results: Of 654 reports, 41 met the study criteria. Five types of arm exercise tests were identified: arm ergometry, ring shifts, dowel lifts, proprioceptive neuromuscular facilitation, and activities of daily living (ADL) tests. Four studies assessed measurement properties of the Unsupported Upper Limb Exercise test (ULEX), 6-minute Pegboard and Ring test (6PBT), a test involving weight shifts and 231s

117. Rehabilitation, outcome measures and effects

P1255
Lower limb fatigue, during walking in patients with COPD
Philippe Gagnon1, Valérie Couta1, Laurent Bouyer2, Cynthia Broscorial1, François Malha1, Didier Sany1. 1Pneumologie, Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, QC, Canada; 2Centre de Recherche, Centre Interdisciplinaire de Recherche en Réadaptation et Intégration Sociale, Quebec, QC, Canada

Background: The contribution of quadriceps muscle fatigue to cycling exercise intolerance is well recognized in COPD. Whether muscle fatigue occurs in plantar and dorsi-flexor muscles during walking is still unknown in these patients.

Aim: To compare muscle strength and fatigue induced by walking exercise in plantar and dorsi-flexor muscles between COPD patients and healthy subjects.

Method: Eleven patients with COPD (FEV1 58±15% predicted) and 11 healthy subjects matched for age and BMI performed a 12-minute walking exercise. The speed and slope of the treadmill were adjusted to achieve a targeted 40 kcal energy expenditure for each subject. Maximal voluntary contraction (MVC) and twitch force (Tw) measured by magnetic stimulation were obtained for plantar and dorsi-flexor muscles prior to and 15 minutes after exercise.

Results: At rest, MVC and Tw tended to be lower in COPD patients compared to healthy subjects for plantar (51±12.8 vs 65±23.7 kg, p=0.08 and 10±9.4±3.7 vs 13±2.6 kg, p=0.09) and dorsi-flexor (24±4.10 vs 33±7.8±4.4 kg, p=0.06 and 4.2±1.4 vs 6±1.2±1.3 kg, p<0.05) muscles. In COPD patients both, MVC and Tw were significantly decreased by 15% after exercise for plantar-flexor (p<0.001), 15±21% (p<0.05) and for dorsi-flexor (4±11% and 31±19%, p<0.05). There was no difference in healthy subjects post-exercise for either plantar-flexor (1±10% and -4±14%), or dorsi-flexor muscles (1±3% and 4±7%).

Conclusion: Muscle weakness and a susceptibility to develop muscle fatigue after walking occur in the patient and dorsi-flexor muscles in patients with COPD compared to controls.

SUNDAY, SEPTEMBER 25TH 2011

Farmaceutici SpA. Visit Chiesi Farmaceutici SpA, at Stand D.30
Farmaceutici SpA. Visit Chiesi Farmaceutici SpA. at Stand D.30

Aim: The work of walking (WOW) can be a better outcome measure of functional capacity. The aims of this study were to compare WOW between patients with cystic fibrosis (CF) and healthy controls, and to determine the factors affecting WOW during 6-minute walk (6MWT) in patients with mild cystic fibrosis.

Materials and methods: Twenty-five mild CF patients (FEV1 88.6±19.2%, 12.6±3.3 years) and 20 healthy subjects (13.8±4.5 years) participated in this study. 6MWT was performed, and WOW calculated as body weight×6MWT distance. Peripheral muscle strength (knee extensors, shoulder flexors, hand grip) were assessed using a dynamometer. Inspiratory and expiratory muscle strength (MIP and MEP) were determined with a mouth pressure device. Fat free mass percent (%FFM) was assessed using skinfold method. Health status were determined with Childhood Health Assessment Questionnaire (CHAQ).

Results: Lung function, WOW, and quadriceps muscle strength were significantly lower in CF patients as compared to healthy subjects (p<0.05). The WOW in 6MWT was significantly related with knee extensor strength (r=0.71), shoulder flexor strength (r=0.65), hand grip strength (r=0.78), MIP (r=0.52), MEP (r=0.64), %FFM (r=-0.38), CHAQ activities of daily living (r=0.56) and total scores (r=0.47, p<0.05). Quadriceps muscle strength and MEP explained 82% variance in WOW in 6MWT.

Conclusion: Quadriceps muscle strength and WOW decrease in mild CF patients. The WOW performed during in a functional capacity test is related to peripheral muscle strength, health status and body composition in CF. Quadriceps muscle strength and MEP are the independent factors determining WOW in CF patients. The work of walking can be used as outcome measure in these patients.

Six minute walk test in obese children and adolescents

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Background: Six minute walk test (6MWT) is an accessible tool to evaluate the submaximal physical capacity. There are few studies that evaluate the 6MWT in obese children and adolescents.

Aim: To compare the performance of obese and healthy children and adolescents in the 6MWT analyzing the walked distance (WD), the work (W) and the efficiency of the metabolic processes during the test.

Method: Comparative, analytical and cross sectional study including, eighty four subjects in the 6MWT analyzing the walked distance (WD), the work (W=body weight × WD) and the metabolic efficiency (%FFM). %FFM was defined according to CDC standards (IMC = body weight/height²). The 6MWT followed the ATS guidelines.

Results: The obese subjects walked a significantly shorter distance than the eu-obese group (p=0.00). There were similar differences between the groups in the PC (p=0.25), %FFM (p=0.32), W (p=0.17), and efficiency of the metabolic processes (%FFM) (p=0.41). The W in the eu-obese group was significantly higher than the healthy group (p=0.00). There were similar differences between the groups in the PC (p=0.25), %FFM (p=0.32), W (p=0.17), and efficiency of the metabolic processes (%FFM) (p=0.41).

Conclusion: The work rate increment during IST in 6MWT has determined a higher exercise tolerance, cardiopulmonary stress and perceived exertion at peak exercise were equivalent between CST and MIST.

Six minute walk test in obese children and adolescents

Mariana Simoes Ferreira, Roberto Teixeira Mendes, Maria Angela G. de Oliveira Ribeiro, Jose Dirceu Ribeiro. Pediatrics, Center for Investigation in Pediatrics, LAFESP/ICPESP, State University of Campinas Medical School, Unicamp, Campinas, Sao Paulo, Brazil

Background: Six minute walk test (6MWT) is an accessible tool to evaluate the submaximal physical capacity. There are few studies that evaluate the 6MWT in obese children and adolescents.

Aim: To compare exercise tolerance time, cardiopulmonary stress, and perception of effort between CST and a modified incremental step test (MIST).

Methods: Thirty-two patients with COPD (FEV1: 50±15% of predicted) underwent the CST and MIST at the same day, an hour apart, on a single step (20 cm of height). Both tests were externally paced by sonorous stimulus previously recorded on a CD. CST started with a rhythm of 15 steps/minute and increments of five steps were performed every two minutes, with a total time of ten minutes. MIST started with 10 steps/minute and increments of one step every 30 seconds until the limit of tolerance.

Results: CST had shorter duration than MIST (42.7±2 min versus 6.4±3 min, respectively; p<0.05) and also lower total number of steps (77.4±51 versus 103.6±30, p<0.05). However, similar cardiopulmonary stress, pulmonary impairment, exercise desaturation and leg fatigue was observed between both tests. Desaturation in both tests and non-desaturation in either tests were observed in five and seven patients, respectively. Among the metabolic and ventilatory variables measured at peak exercise, higher oxygen uptake and lower ventilatory equivalent for oxygen were observed for IST as compared to MIST (1.5±0.3 L/min versus 1.2±0.4 L/min and 33.5±7.4 vs 36.3±7.8; p<0.05). The recovery time was longer in MIST as compared to CST (1.1±0.2 min versus 0.5±0.2 min, p<0.05). The recovery time was longer in MIST as compared to CST (1.1±0.2 min versus 0.5±0.2 min, p<0.05). The recovery time was longer in MIST as compared to CST (1.1±0.2 min versus 0.5±0.2 min, p<0.05).

Conclusion: The desaturation was detected only during IST in 33% of patients. VO2 peak is higher, ventilatory demand is lower and desaturation more pronounced during stepping than cycling.

Six minute walk test in obese children and adolescents

Mariana Simoes Ferreira, Roberto Teixeira Mendes, Maria Angela G. de Oliveira Ribeiro, Jose Dirceu Ribeiro. Pediatrics, Center for Investigation in Pediatrics, LAFESP/ICPESP, State University of Campinas Medical School, Unicamp, Campinas, Sao Paulo, Brazil

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P1264
The modified version of the pulmonary functional status and dyspnea questionnaire: A valid measure to evaluate functional status in patients with COPD

Chris Burtn1,2, Daniel Langer1,2, Hans Van Remoortel1,2, Rik Gosselink1,2

Background: The modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M) is a reliable tool which aims to evaluate perceived functional status in patients with chronic obstructive pulmonary disease (COPD).

Aim: To establish the MID of PFSDQ-M using different approaches.

Methods: 461 patients with COPD (FEV1 ≥ 42% predicted) completed the PFSDQ-M before and after a 3-month pulmonary rehabilitation program (ΔCRDQ +16±1.5points, Δ6MWD +45±8.9m, both p<0.001). The correlation between the ΔPFSDQ-M and the anchors ΔCRDQ and Δ6MWD was calculated. When r ≥ 0.3 linear regression analyses were performed to predict the MID from these anchors (i.e. establish the ΔPFSDQ corresponding with 10points ΔCRDQ, 2.5points Δ6MWD). The PFSDQ was also applied in the distribution-based Cohen’s effect size technique to confirm the MID.

Results: Anchor and distribution - based methods estimates are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Method</th>
<th>MID of PFSDQ-M (95% CI) Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchor Based</td>
<td>CRDQ dyspnea score (MID=2.5)</td>
<td>-5 to -3</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-4 to -2</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-3 to -1</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-1 to 0</td>
</tr>
<tr>
<td>CRDQ total score (MID=10)</td>
<td>-4 to -2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-5 to -3</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-3 to -1</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-1 to 0</td>
</tr>
<tr>
<td>6MWD (MID=30)</td>
<td>-5 to -3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-6 to -4</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-4 to -2</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-2 to 0</td>
</tr>
<tr>
<td>Distribution Based</td>
<td>Cohen effect size activity</td>
<td>0.5 ± 0.3</td>
</tr>
</tbody>
</table>

Conclusion: The MID of the PFSDQ-M ranged from -3 to -6 points in patients with moderate to very severe COPD. The estimate was similar with both statistical techniques.

ER is a fellow of CAFES 14/15/10-3.

P1265
The minimal important difference of the pulmonary functional status and dyspnea questionnaire – Modified version in patients with COPD

Eloisa Regueiro1,2,4, Chris Burtin1,2, Daniel Langer1,2, Hans Van Remoortel1,2, Paul Baten1, Valeria Pires Di Lorenzo1,2,3, Dirceu Costa1,2, Wim Janssens4, Marc Decramer1,2, Rik Gosselink1,2, Thierry Troosters1,2

Background: The modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M) is commonly used in COPD to obtain information about their symptoms and functional status. It has been shown to be responsive to change following pulmonary rehabilitation. The minimal important difference (MID) of the PFSDQ has never been established.

Aim: To establish the MID of PFSDQ-M using different approaches.

Methods: 416 patients with COPD (FEV1 42±12points, Δ6MWD 45±8.9m, both p<0.001). The correlation between the ΔPFSDQ-M and the anchors ΔCRDQ and Δ6MWD was calculated. When r ≥ 0.3 linear regression analyses were performed to predict the MID from these anchors (i.e. establish the ΔPFSDQ corresponding with 10points ΔCRDQ, 2.5points Δ6MWD). We also applied the distribution-based Cohen’s effect size technique to confirm the MID.

Results: Anchor and distribution - based methods estimates are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Method</th>
<th>MID of PFSDQ-M (95% CI) Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchor Based</td>
<td>CRDQ dyspnea score (MID=2.5)</td>
<td>-5 to -3</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-4 to -2</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-3 to -1</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-1 to 0</td>
</tr>
<tr>
<td>CRDQ total score (MID=10)</td>
<td>-4 to -2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-5 to -3</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-3 to -1</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-1 to 0</td>
</tr>
<tr>
<td>6MWD (MID=30)</td>
<td>-5 to -3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>-6 to -4</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>-4 to -2</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td>-2 to 0</td>
</tr>
<tr>
<td>Distribution Based</td>
<td>Cohen effect size activity</td>
<td>0.5 ± 0.3</td>
</tr>
</tbody>
</table>

Conclusion: These findings add to the validity of the PFSDQ-M as a subjective tool to evaluate functional status in patients with COPD.

P1265
Anxiety and depression in patients referred for pulmonary rehabilitation

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Introduction: Psychological morbidity is well recognised in chronic respiratory disease, but the effect of uptake, completion and response to pulmonary rehabilitation (PR) is unknown.

Method: In 302 consecutive patients referred to an 8-week outpatient PR program, the Hospital Anxiety and Depression Score (HADS) was used to assess symptoms of anxiety and depression. A HADS domain score of ≥21 identified patients with moderate levels of anxiety and depression. Subsequent uptake and compliance with PR was recorded. Pre- to post-PR changes in incremental shuttle walk (ISW) and self-reported Chronic Respiratory Disease Questionnaire (CRDQ) were compared between those with moderate anxiety (ANX) or moderate depression (DEP), and those without, defined as HADS ≤ 7 (NA and ND).

Results: 71 (23.5%) and 59 (19.5%) patients had evidence of moderate anxiety and depression respectively. 22 (31%) of ANX and 21 (36%) of DEP either failed to start or complete PR. Despite similar FEV1% predicted, ANX had significantly impaired baseline ISW (median 100 vs. 180 m; p<0.01) and health status (CRDQ: SR 55 vs. 86) compared to the NA group. There was no significant difference in median pre- to post-PR change in ISW and CRDQ between ANX and NA completers. Similarly, the DEP group had comparable FEV1% predicted to ND, but had significantly impaired baseline median ISW (90 vs. 200 m; p<0.01) and mean CRDQ (53 vs. 84; p<0.01). However ISW and CRDQ response to PR was similar between DEP and ND.

Conclusion: Significant psychological morbidity is prevalent in patients referred to PR. Over 30% fail to start or complete PR. These patients also have impaired exercise capacity and quality of life, but completers respond normally to PR.

P1266
Breathlessness is associated with lower completion rates of pulmonary rehabilitation classes

Victoria Lord1, Melanie Thomas1, Joerg Steier1, Nicholas Hopkinson2

Background: It is important to develop specific approaches to improve completion rates in pulmonary rehabilitation (PR). Currently, it is not clear what parameters predict completion & non-completion. We hypothesised that specific demographic parameters are associated with completion rates of PR.

Methods: Respiratory patients who commenced PR classes at the Royal Brompton Hospital from September 2007 were included. At assessment we recorded age, MRC dyspnoea score, FEV1 (% pred), FVC & body mass index. Completion was defined as attendance of 12 or more out of 16 sessions. T-tests and logistic regression tests were performed on the variables.

Results: Data was available for 167 patients (77 females, mean (SD) age 66 (9.7) yrs, FEV1, 1.15 (0.6) litres (46.1% pred (21.3)), MRC 3 (1). We included a range of diseases (122 COPD, 16 bronchiectasis, 12 ashma, 14 restrictive disease and 3 normal sprirometry). The 105 patients who completed PR had a lower baseline MRC dyspnoea score, which was significant. The remaining tested parameters were not independent associated with completion rate. Of the non-completers 37% failed to attend classes and 21% stopped due to an exacerbation. Completion rates were not different in those with or without COPD.

Demographics of patients in the completion and non-completion groups

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>66.8 (9.9)</td>
<td>64.8 (9.2)</td>
</tr>
<tr>
<td>Non-Complete</td>
<td>65.4 (11.6)</td>
<td>63.5 (11.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (5.6)</td>
<td>27.4 (6.8)</td>
</tr>
<tr>
<td>MVC (l)</td>
<td>1.15 (0.61)</td>
<td>1.14 (0.61)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>46.7 (22.4)</td>
<td>45.2 (19.2)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.37 (0.89)</td>
<td>2.36 (0.91)</td>
</tr>
</tbody>
</table>

Conclusion: A more tailored approach to improve completion rate of PR classes may need to focus on the more breathless & exacerbating patients.
Conclusion: NLR muscle training optimizes exercise and muscle training programs in patients with low FFM and more advanced COPD.

P1269 Pulmonary rehabilitation: Investigating the characteristics and use of a warm-up

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Background: Exercise training is recognised as an essential component of pulmonary rehabilitation (PR). Guidelines however do not detail a warm-up phase although evidence when prescribing any form of physical activity considers warming up as fundamental for optimal performance. Warm-up structure should relate to the subsequent tasks and consider individual capabilities. Particular attention is therefore required in PR that participants are warmed-up but not fatigued before exercise training.

Aims and objectives: To investigate current practice in PR, considering specific characteristics and use of a warm-up phase.

Methods: An online, prospective, cross-sectional survey using questionnaires disseminated through Physiotherapy networks in the UK.

Results: All 52 respondents reported use of a warm-up. The majority included upper and lower limb movements integrated with low intensity aerobic exercise. Marching on the spot was the predominant activity reported but also thoracic rotations (23%), walking (12%) and lateral trunk flexion (14%). Stretching was integrated into all programmes. Warm-ups lasted between 6-10 minutes for 51% (range: 3-15 minutes). Modified Borg Scale of Perceived Breathlessness was used by 12% to determine warm up intensity. However, 29% reported participants frequently failed to complete the warm-up, with 88% limited by breathlessness.

Conclusions: All surveyed PR programmes report the inclusion of a warm-up phase though with considerable variability regarding content, duration, and intensity. Individuals however may fail to complete due to breathlessness. Further research is required to determine how warm-ups in PR can be effectively structured for maximum participant benefit.

P1270 The effect of pulmonary rehabilitation programme in patients with pulmonary sarcoidosis

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Background: Pulmonary rehabilitation (PR) has proven effective in treatment of COPD patients. The effectivity of PR in patients with pulmonary sarcoidosis remains unclear and therefore there is a need for further research.

Aim: To evaluate the effect of PR on breathing pattern and health-related quality of life (HRQL) in patients with pulmonary sarcoidosis.

Methods: There were 10 patients with pulmonary sarcoidosis recruited to the 6-week PR programme. The assessment included lung function tests, maximal inspiratory (MIP) and expiratory (MEP) mouth pressures, chest expansion (CE), 6-minute walking test (6MWT) and HRQL by Sarcoidosis Health Questionnaire (SHQ). The evaluation was performed at baseline and after six weeks. The PR programme consisted of respiratory physiotherapy, soft tissue techniques and regular physical activity.

Results: The mean age of patients was 45.9±14.1 years with stages I, II and III of the disease (2, 7 and 1 patient respectively). Six patients were undergoing PR programme simultaneously with corticotherapy. Lung function tests showed normal values in all patients at baseline and after PR.

Conclusion: Patients with pulmonary sarcoidosis can benefit from a PR programme, as it improves chest expansion and strength of breathing muscles, which plays an important role in the physical fitness level and is further reflected in an improved HRQL of the patients. Supported by Palacky University, FTK_2010_004.

P1271 The effect of an 8-week outpatient rehabilitation programme on chest expansion and ventilatory parameters in patients with COPD

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Background: Dysfunction of the breathing mechanisms could lead to an increased
inspiratory effort and to a higher prevalence of breathing disorders during activities of daily living in patients with COPD.

Aim: To assess whether patients with COPD have different chest expansion (CE) in comparison with healthy controls and whether the rehabilitation programme (RP) can influence CE and ventilatory parameters in COPD patients.

Methods: The examined group consisted of 36 medically stable adults with COPD (aged 62.9±6.7 years, stage II) who have undergone an 8-week outpatient RP (breathing and postural control exercises, airway clearance techniques and soft tissue techniques) and 30 healthy controls (aged 63.3±3.0 years). Lung function test and CE were measured at baseline and after 8 weeks.

Results: COPD patients had significantly reduced CE in comparison with control group at baseline. CE was significantly higher after RP in patients with COPD and there was no significant difference among control group and COPD patients after RP.

There was an improvement of ventilatory parameters in COPD patients after RP, although the severity of the peripheral airway obstruction remained at the same level.

<table>
<thead>
<tr>
<th>Mean improvement (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>9.4</td>
</tr>
<tr>
<td>FEV1</td>
<td>9.1</td>
</tr>
<tr>
<td>PEF</td>
<td>10.3</td>
</tr>
<tr>
<td>MEF25</td>
<td>3.4</td>
</tr>
<tr>
<td>MEF50</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Conclusion: Our results show that physiotherapy treatment approaches can influence chest mobility and improve breathing mechanisms in COPD patients.

118. Respiratory physiotherapy in the intensive care unit and on the ward: breathing exercises and respiratory muscles

P1274
The inter-observer agreement of handheld dynamometry in critically ill patients
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Objective: Muscle weakness is associated with increased risk of morbidity, mortality and limiting functional outcome. To assess muscle weakness reliable measurements are required. The objective is to determine inter-observer reliability of handheld dynamometry (HHD) in awake and cooperative critically ill (CI) patients.

Patients: A cross sectional, randomly selected sample of CI patients.

Measurements: HHD was performed in CI patients, who had at least a score of 3 on the Medical Research Council scale. 3 Upper limb and 3 lower limb muscle groups were tested at the right hand side. Patients were tested twice daily by 2 independent raters.

Results: 51 test-retests were performed in 39 CI patients. Strength was considerably reduced compared to the predicted value: shoulder abduction 43% pred (IQR: 35-56); elbow flexion 38% pred (IQR: 23-58); wrist extension 51% pred (IQR: 35-56).

P1273
Pulmonary rehabilitation: Are the effects similar in populations from different countries?
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Background: There are no studies investigating whether differences in socioeconomic, ethnic or climate characteristics could interfere with outcomes of pulmonary rehabilitation (PR) programs.

Objective: To compare the training effects of similar exercise training programs applied to two groups of patients with chronic obstructive pulmonary disease (COPD) living in different world regions: one from Western Europe (Belgium) and another from South America (Brazil).

Methods: 564 patients with moderate to severe COPD (45 in Brazil and 519 in Belgium) underwent similar high-intensity outpatient PR programs. Baseline values and their respective post-training changes of pulmonary function, exercise capacity, physical activities in daily life, respiratory muscle force, health-related quality of life (HRQoL) and functional status were compared between centers.

Results: Patients were matched for age, BMI and FEV1. Baseline differences were found in the 6-minute walking test (67.4±12%pred in Brazil vs 57±20%pred in Belgium; p<0.01), inspiratory muscle force (96±28cmH2O in Brazil vs 143±48cmH2O in Belgium; p<0.01) and functional status (all domains had better scores in Brazil in the Modified Pulmonary Functional Status and Dyspnea questionnaire; p<0.01). After 3 months of training, only the dyspnea domain of the Chronic Respiratory Disease Questionnaire showed significant difference between centers (0.50 [2 – 5] in Brazil vs 5 [2 – 8] in Belgium; p<0.01).

Conclusions: Similar PR programs applied in populations from different countries yield similar improvements in exercise capacity, respiratory muscle function, functional status and most HRQoL outcomes. Dyspnea was more enhanced in Belgian patients.

References:
P1275
Effects noninvasive mechanical ventilation on muscle strength, ambulation, and functional performance in the intensive care
Sahveren Cakartas1, Farid Bazarri2, Caroline Jolley1, Lizzie Flude1, Victoria Lord1, Mike Polkey1, Nick Hopkinson2, Mike Polkey1, Nick Hopkinson2, Mike Polkey1, Nick Hopkinson2.
1Respiratory Research Unit, The Royal Brompton and Harefield NHS Trust, London, United Kingdom; 2NHR Respiratory Disease Biomedical Research Unit, The Royal Brompton & Harefield NHS Trust, London, United Kingdom.

Introduction: Patients with acute exacerbations of chronic respiratory disease are often too breathless to exercise leading to muscle deconditioning. Using NIV to assist exercise during an exacerbation might prevent this but it is not known if this is acceptable to patients.

Methods: 10-in-patients with an acute exacerbation (including COPD, Bronchiec-
tasis, CF) were recruited. If they were unable to cycle for 5 minutes at 20 watts unaassociated they then cycled with NIV for up to 20 minutes. NIV settings were ad-
justed to patient comfort. Oxygen was titrated to maintain SpO2 88-92%. Patients were asked to rate their level of distress and willingness to repeat the intervention.

Results: Mean age was 52.8 (15.9). 56% male: 67% used NIV at night. All were naive to NIV during exercise. NIV increased cycle time by 90 seconds (47.8%). All stated they would repeat this type of exercise and most (90%) reported it easier to exercise with NIV.

<table>
<thead>
<tr>
<th>Without NIV</th>
<th>With NIV</th>
<th>Difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time cycled (mins)</td>
<td>3.18 (1.35)</td>
<td>4.7 (1.30)</td>
<td>1.52 (0.32 to 2.72)</td>
</tr>
<tr>
<td>Respiration SpO2</td>
<td>94 (3.89)</td>
<td>96 (2.26)</td>
<td>2.4 (–0.46 to 0.63)</td>
</tr>
<tr>
<td>Respiration HR</td>
<td>102 (14.87)</td>
<td>100 (16.19)</td>
<td>2.50 (–0.42 to 9.42)</td>
</tr>
<tr>
<td>Change in SpO2</td>
<td>–3.4 (4.72)</td>
<td>1.90 (3.35)</td>
<td>5.30 (0.89 to 9.71)</td>
</tr>
<tr>
<td>Change in HR</td>
<td>9.1 (7.99)</td>
<td>12.60 (7.35)</td>
<td>3.50 (–4.22 to 11.22)</td>
</tr>
<tr>
<td>End Borg (hypoxia)</td>
<td>4.67 (1.86)</td>
<td>3.92 (0.67)</td>
<td>–0.75 (–2.79 to 1.29)</td>
</tr>
<tr>
<td>End Borg (hypercapnia)</td>
<td>12.50 (2.88)</td>
<td>11.00 (3.16)</td>
<td>–1.50 (–4.05 to 1.05)</td>
</tr>
</tbody>
</table>

All data presented as mean (SD). *Paired t-test

Conclusion: NIV is well tolerated, feasible and significantly increases exercise capacity in patients hospitalised with an acute exacerbation.

P1279
Is there a need for training when using an oscillatory positive expiratory pressure device?
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Introduction: Oscillatory positive expiratory pressure with Acapella® is routinely used to remove secretions. The system uses a counterweighted plug and a magnet to generate pressure and airflow oscillations. To be efficient, this pressure must be higher than 10 cm H2O. There is no recommendation about the instructions for the patient and the interface (mouthpiece or facemask) to use with the system. The aim of this study was to measure the pressure generated by subjects after basic instructions.

Material and method: Eight healthy subjects (28.7 yrs. ± 8.0) were recruited. They were instructed to breathe through Acapella® with two interfaces (mouthpiece and facemask) and with different resistance settings in a randomized crossover design. Continuous recordings of airway pressure and airflow were performed. Sequence was composed by 5 breathes at each resistance setting. Success rate was defined as an expiratory pressure higher than 10 cm H2O.

Results: Depending on interface, significant differences (mouthpiece vs face-
mask) were measured for Pe max (11.23 cm H2O±3.6 vs 10.3 cm H2O±2.52; p=0.001). Pe (6.67 cm H2O±1.58 vs 6.2 cm H2O±1.43; p=0.001), inspiri-
tory flow (3.04±0.94 vs 3.47±1.11; p=0.001) and expiratory flow (5.64±0.05 vs 6.23±0.01; p=0.001). Time spent with Pe ≥ 10 cm H2O (1.24±1.33 vs 236s)
P1280 Validation of a time-frequency wheeze detector in cystic fibrosis: A pilot study

Tomas Miguel3, Celedonia Igual Camacho 1, Juan Carlos Meléndez Moral 4, Jon Thomas Ellingsen4, Ola Røksund 3,5.

Objective: This pilot study aimed to validate a time-frequency wheeze detector (TF-WD) in the cystic fibrosis disease.

Methods: Recordings were made in a clinical setting from a stable cystic fibrosis adult outpatient with a digital stethoscope following the CORSA guidelines. Several TF-WD algorithms were tested and the best performance was obtained with the Taplidou et al. (2007) algorithm, which was validated in four sound files. The number, duration and type of wheezes were blindly analysed independently by three experienced respiratory physiotherapists. Their evaluation was then compared with the automatic method. The statistics accuracy of the wheezes detection was quantified through sensitivity, specificity and performance measures using Matlab. True positives/negatives and false positives/negatives were counted by comparing each point of the sound file.

Results: Inter-rater agreement between the physiotherapists was 96.9%. The sensitivity, specificity and performance of the automated method were 77.2%, 98.4% and 87.1% respectively.

Conclusion: The automated method tested shows sufficient reliability to continue the study and implement a future clinical validation with a larger sample. Wheezes detection through computerized analysis can provide an objective measure to assess and monitor cystic fibrosis patients, however further research is needed to validate the most robust algorithm.

P1281 Randomized clinical trial: Effects of controlled breathing exercises on respiratory muscle in the elderly

Maria Angeles Cebrià i Iranzo1, David Alan Arnall2, José Manuel Tomás Miguel3, Celedonia Igual Camacho1, Juan Carlos Meléndez Moral1, Jon Roger Web1.

Introduction: Respiratory muscle (RM) strength decreases with aging, and in most cases this decrease is associated with functional impairment and disabilities, particularly in the frail elderly. RM training has been shown to improve RM strength. The purpose of this study was to assess the effect of controlled breathing exercises on RM strength among elderly people with disabilities who are unable to engage in general exercise reconditioning. The hypothesis is that controlled breathing exercises will improve RM strength vs. a control group.

Methods: Forty-eight elderly were randomly assigned to a control group (n=24) or training group (n=24). A supervised training protocol, consisting of controlled Pranayama breathing exercises, was performed 5 times per week for 6 weeks. Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were assessed at 4 time points: pre-test, intermediate, post-test and follow-up.

Results: The anthropometrics, pulmonary function and RM function data of participants did not showed significant differences between groups. ANOVAs revealed significant differences in MIP and MEP between the two groups after the training protocol. For MIP the effect was effective (F3,138=9.122, p<0.001, η²=0.165). Also for MEP is statistically significant (F3,138=9.02, p<0.001, η²=0.165).

Conclusions: This is the first controlled study in elderly people that report a significant gain in RM strength due to the Pranayama training program.

P1282 Laryngeal movements during mechanical insufflation-exsufflation

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Introduction: Mechanical insufflation-exsufflation (MI-E) is the most effective approach to increase peak cough flow in patients with neuromuscular diseases, thereby potentially augmenting airway clearance. Co-ordinated movements of the vocal cords and laryngeal false and true vocal cords are crucial for effective coughing. Thus, laryngeal response patterns to MI-E have not been studied.

Objectives: To validate the laryngeal response patterns to MI-E in healthy subjects.

Methods: Ten healthy volunteers (21-26 years) were examined with video recorded flexibl transnasal fiberoptic laryngoscopy during MI-E (Cough Assist®, Respiration, USA) according to a standardized protocol at pressures of ±20 to ±50 cmH2O. Participants were instructed to inhale during insufflation and to cough or actively exhale during exsufflation. Laryngeal patency and movements during MI-E was assessed from video recordings according to a pre-set scheme.

Results: In all subjects and regardless of the applied pressure and instructions, the vocal cords ab ducted during insufflation and exsufflation. Coordinated glottic closure and opening on instruction to cough was found in 10/10. At exsufflation pressures of ±40 to ±50 cmH2O, hypopharyngeal obstruction was observed in 10/10. Cough presented as sequential glottic closures in the majority. Retroflex movement of the epiglottis, partially occluding the laryngeal entrance, was observed in three subjects during insufflation, irrespective of pressures.

Conclusion: The laryngeal response patterns to MI-E in healthy subjects was as described for spontaneous cough. Negative pressures may cause temporary hypopharyngeal obstruction, and retroflex movement of the epiglottis may obstruct airflow. The examination was well tolerated and may be considered for use in patients.
The assessment of the maximum inspiratory pressure (MIP) is used as an indicator of inspiratory muscle strength and may be useful in evaluating the success of weaning from mechanical ventilation. During this procedure it is common that a fall of saturation peripheral O2 (SpO2) occurs, leading to discontinuation of the maneuver, which can underestimate the value of MIP. The objective of this study is to verify whether the implementation of hyperoxegenation prior to the assessment can mitigate this decline of SpO2, increasing the measurement support time (t,), and generating a more reliable MIP.

The evaluation of the MIP, occlusion time (OT), SpO2, respiratory rate (RR) and heart rate (HR) was carried out randomly on 26 patients, with or without hyperoxegenation prior, maintaining the duration of occlusion of unidirectional valve for an indefinite period. Hyperoxegenation was defined as the use of inspired oxygen fraction (FiO2) to 100%, two minutes before the maneuver. The measurement was performed with the patient in the supine position and elevated head with an angle of 60°.

The value of MIP and OT were higher with previous hyperoxegenation (53.77±22.37 cmH2O vs 43.38±20.11 cmH2O; p<0.001; and 58.69±26.09 sec vs 37.04±15.07 sec;p< 0.001; respectively). In addition, there was a smaller drop in SpO2 after the measurement when the method was performed with hyperoxegenation (93.15±1.24% vs 84.58±9.73%;p<0.001). There was increase in RR and HR independently of the hyperoxegenation.

Implementation of hyperoxegenation prior to the assessment of MIP increase the values obtained, generating a more reliable MIP.
lung function in the postoperative period. Aiming to attenuate these negative effects, the preoperative IMT may be an alternative.

Objective: To determine whether preoperative IMT is able to attenuate the impact of surgical trauma on the diaphragmatic excursion in obese women undergoing OBS.

Methods: Thirty-two obese women (35.4±8.75 years and 41.78±3.84 kg/m²), undergoing elective OBS were randomly assigned to receive preoperative IMT (IMT group) (n=15) or usual care (Control group - CG) (n=17) 2.4 weeks before the surgery. The diaphragmatic excursion was evaluated using the digitalized image of the radiograph. The area was calculated of the right and the left dome of the diaphragm. The patients were assessed before and after training, and 1 day after surgery.

Results: The diaphragmatic excursion of the right and the left dome were not altered by training. In the first postoperative day, there was a significant decrease in both groups. However, the values of diaphragmatic excursion were higher in the IMT group, even though they were not statistically significant.

Conclusion: The preoperative IMT appears to attenuate the negative postoperative effects of open bariatric surgery in diaphragmatic excursion.


P1290
Effects of preoperative inspiratory muscle training (IMT) in obese women undergoing open bariatric surgery: Respiratory muscle strength

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Introduction: Patients undergoing open bariatric surgery have an impaired lung function in the postoperative period. Aiming to attenuate these negative effects, the preoperative IMT may be an alternative.

Objective: To determine whether preoperative IMT is able to attenuate the impact of surgical trauma on the respiratory muscle strength in obese women undergoing open bariatric surgery.

Methods: This study is a randomized controlled trial. Thirty-two obese women (35.4±8.75 years and 41.78±3.84 kg/m²), undergoing elective open bariatric surgery were randomly assigned to receive preoperative inspiratory muscle training (IMT group) (n=15) or usual care (UC group) (n=17) 2.4 weeks before the surgery. The respiratory muscle strength was carried out by using measurement the Maximal Inspiratory and Expiratory Pressures – MIP and MEP. The patients were assessed before training, before surgery and 1 day after surgery.

Results: After training, there was an increase in the MIP only in the IMT group (IMT=93.3±23.80 to 120.1±20.35 vs UC= 92.9±18.63 to 91.76±20.38 cmH2O – p<0.05). The MEP was not altered by training. In the first postoperative day, there was a significant decrease in MEP in both the groups. However, the MEP was higher in the IMT group (IMT = 63.3±21.60 vs UC = 48.8±19.32 cmH2O – p<0.05). The MEP was similar between the groups (IMT=49.66±22.71 vs UC= 49.70±39 cmH2O).

Conclusion: The preoperative IMT increased the inspiratory muscle strength (MIP) and attenuated the negative postoperative effects of open bariatric surgery in obese women for this variable, though not influencing the MEP.


P1291
Inspiratory muscle strength and endurance in patients with COPD: A propose outcome with manovacuometry and PowerBreathe®

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Background: Reduced respiratory muscle force and endurance are commonly observed in patients with COPD and contributes to dyspnea, oxygen desaturation and reduced exercise capacity, hence respiratory muscle assessment is clinically relevant.

Aim: To propose an assessment method of respiratory muscle endurance in patients with COPD and to verify it relationship with maximal inspiratory pressure (MIP) and maximal voluntary ventilation (MVV).

Method: 18 patients (GOLD I-4; 63±9years) performed the MIP and an incremental and constant respiratory muscle endurance test using the PowerBreathe® device. The incremental test started with 10cmH2O, increasing 10cmH2O each 2min, with 1min of rest between them, which determined the maximal pressure sustained (MPS). The endurance test was 80% of the MPS. The limit time (lim) was determined. Comparisons and correlations were determined using Paired t-test and Pearson correlation.

Results: The MIP was 52±20cmH2O, MVV (Spred) 44±15, MPS 48±23cmH2O, tim 10±8 min and 80%MPS 35±21cmH2O. The MIP and MPS were not different. Correlation was found between MIP and MPS (r=0.5; p=0.03) and MIP and MVV (r=0.6; p=0.03).

Conclusion: The MIP and MEP were similar in the endurance test and showed a relationship with MVV; with suggest to be a reasonable test to assess the respiratory performance in these patients.

Funding: CAPES - Brazil

P1292
Respiratory muscle function during and after a severe exacerbation of COPD – Preliminary results

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Background: It is known that peripheral muscle function (especially the quadriceps muscle function) is markedly reduced during the course of a severe exacerbation of chronic obstructive pulmonary disease (COPD). However, the function of the respiratory muscles has not been studied in depth in the same context.

Objectives: To investigate the respiratory muscle function during and after a severe exacerbation of COPD requiring hospitalization.

Methods: Twelve patients with COPD (7 male, 68±14 years, forced expiratory volume in the first second [FEV1], 37±22%pred) hospitalized due to an acute exacerbation of COPD were studied. Inspiratory and expiratory muscle strength (PImax and PEmax, respectively) were assessed at day 1 and day 3 of hospitalization and at hospital discharge, as well as at 1 month after discharge (1MD). Lung function was assessed at day 1, at discharge and at 1MD.

Results: PImax was significantly reduced at day 1, day 3 and at discharge in comparison to 1MD (p<0.05 for all), although it tended to improve overtime during the hospitalization period. PEmax improved significantly overtime during the hospitalization period, while lung function was not significantly altered. Delta PImax%pred (1MD minus day 1) correlated significantly with age (r=0.72), while delta PEmax%pred (discharge minus day 1) correlated significantly with PaCO2 assessed at day 1 (r=0.75).

Conclusions: These preliminary data suggest that the respiratory muscle function is markedly reduced at the onset of a severe exacerbation of COPD. However, unlike the quadriceps muscle, respiratory muscles markedly improve their function during the hospitalization period and during the following month.

P1293
Maximal sniff nasal inspiratory pressure in Brazilian healthy subjects: A multicentre study

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Objective: To propose reference values of SNIP for Brazilian population.

Methods: This study was conducted in three centers in Brazil, Natal-RN, Recife-PF and Piracicaba-SP. Subject were evaluated in relation to anthropometrics parameters, physical activity profile and maximal sniff nasal inspiratory pressure follow recommendations of ATS/ERS Statement on Respiratory Muscle Testing. SNIP

Background: Reduced respiratory muscle function and endurance are commonly observed in patients with COPD and contributes to dyspnea, oxygen desaturation and reduced exercise capacity, hence respiratory muscle assessment is clinically relevant.

Aim: To propose an assessment method of respiratory muscle endurance in patients with COPD and to verify it relationship with maximal inspiratory pressure (MIP) and maximal voluntary ventilation (MVV).

Method: 18 patients (GOLD I-4; 63±9years) performed the MIP and an incremental and constant respiratory muscle endurance test using the PowerBreathe® device. The incremental test started with 10cmH2O, increasing 10cmH2O each 2min, with 1min of rest between them, which determined the maximal pressure sustained (MPS). The endurance test was 80% of the MPS. The limit time (lim) was determined. Comparisons and correlations were determined using Paired t-test and Pearson correlation.

Results: The MIP was 52±20cmH2O, MVV (Spred) 44±15, MPS 48±23cmH2O, tim 10±8 min and 80%MPS 35±21cmH2O. The MIP and MPS were not different. Correlation was found between MIP and MPS (r=0.5; p=0.03) and MIP and MVV (r=0.6; p=0.03).

Conclusion: The MIP and MEP were similar in the endurance test and showed a relationship with MVV; with suggest to be a reasonable test to assess the respiratory performance in these patients.

Funding: CAPES - Brazil

Funding: CAPES - Brazil
was measured from FRC in the sitting positions using a catheter through a plug occluding one nostril during 10 maximal sniffs through the contra-lateral nostril. For each test the largest pressure measured in cmH2O was taken into account. Correlation and multiple linear regressions were used to predicted male and female SNIP equations. Results were compared with previous published studies. Results: We studied 244 subjects (114 male and 130 female) distributed in different age groups 20-80 years old. We found a significantly negative correlation between SNIP and age for male and female (p=0.05). In a multiple regression analysis age continued to have an independent predictive role with SNIP. The predicted equations found for male and females were respectively SNIP = –0.46 age + 135.5 and SNIP = –0.34 age + 109.6. Conclusion: The results of this study provide reference equations for SNIP for health Brazilian population from 20 to 80 years old. Financial support: CNPq.

119. Asthma: issues in rehabilitation and physical therapy

P1294 Late-breaking abstract: Determination of the endurance capacity on resistance exercise – Physiological responses during load-duration relationship

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Resistance exercise (RE) has been strongly encouraged, providing a favorable effect on muscular strength and endurance, cardiovascular function, metabolism and cardiovascular risk reduction. However, little is known about cardiovascular, ventilatory, and metabolic adjustments in the critical load (CL), which would allow the transition of moderate exercise for intense exercise. So, the objectives of the study were to: 1) determine the existence and intensity of critical load (CL) during RE; 2) determine the execution time of CL, and 3) evaluate the behavior of cardiovascular, respiratory and metabolic responses during RE at different intensities and at the CL. Fifteen healthy young men (23±2.5 years) carried out 1 repetition maximum (IRM) on the RE at different percentages of IRM (60%, 75% and 90% IRM) in order to obtain CL by linear regression: load X reverse of time until fatigue (Tlim). Heart rate (HR), blood lactate ([La]), metabolic and ventilatory parameters were measured all resistances loads. The execution time and number of repetitions was different amongst the resistance intensities (p<0.001). All exercises intensities significantly increased (p<0.001): HR, systolic blood pressure (SBP) (p<0.001) and [La] when compared to both rest and recovery. [La] corrected by Tlim was significantly higher during maneuvers at a greater resistance (p<0.0001). However, metabolic and ventilatory measurements were stable with IRM and the time until fatigue (p<0.05). Lastly, the CL during RE was approximately 54% IRM. In our study we characterize CL as the exercise intensity that shows peak values of 83% VO2max and 90% HRmax.

P1295 Late-breaking abstract: Evaluation and comparison of functional capacity to incremental shuttle walk test and maximal exercising test on treadmill in obese women

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The Incremental Shuttle Walk Test (ISWT) has been increasingly used and may constitute a method for assessing functional capacity in obese population. However, if ISWT represents maximal exercise effort and produces similar cardiorespiratory responses in obese women remains to be investigated. The aims was compare the cardiorespiratory responses between obese and eutrophic during the ISWT and the cardiopulmonary exercise testing (CPET). Twenty-nine women (17 obese), allocated in the obese group (OG) and eutrophic group (EG), performed two ISWT and a CPET on a treadmill (Bruce protocol). Heart rate (HR) was determined before and after each test. Ventilatory (VE) and metabolic (VO2; VCO2) measurements were collected breath by breath with a portable ergospirometer (Oxycon mobile; CareFusion-Germany). We considered the results of the second ISWT to statistical analysis. Oxygen uptake (ml/kg/min) as well as distance walked and time of the test were significantly lower in the OG in both tests (ISWT: p<0.001, <0.001, <0.001; CPET: p<0.001, =0.016, <0.001, respectively). Both tests showed correlation between distance and VO2 (ml/kg/min) and HR (ISWT: r=0.83, p<0.001; CPET: r=0.53, p=0.52, respectively). Comparing the methods the ISWT was able to elicit ventilatory, metabolic and cardiovascular responses in agreement with CPET. In addition, it was observed the agreement of both tests to identify relative VO2, VE and HR at the peak of exercise. The ISWT seemed to be an adequate method between obese women and promote ventilatory, metabolic and cardiopulmonary responses in agreement to the CPET. Grants: FAEPESP (09/01842-0, 10/03030-0).

P1296 Level of agreement between five asthma control questionnaires

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Introduction: The Global Initiative for Asthma (GINA) guideline outlines the importance of a total control of asthma. This control is assessed by questionnaires evaluating symptoms, reliever use and functional results. Our study compared 5 different questionnaires and evaluated the degree of agreement between them. Methods: Successive asthma patients with a more than 3 months diagnosis were recruited at our out-patient clinic. They were asked to complete consecutively 5 asthma control questionnaires (GINA, ACQ, ACT, ADAQ, RCP) in a random order. Spirometry and exhaled nitric oxide were also measured. The GINA score was considered as the reference test and compared to the four others using the kappa statistic. For comparison with the ACT and RCP questionnaire, the “partly controlled” level GINA questionnaire was considered as “uncontrolled”. Results: Eighty patients (1.61 female for 1 male) aged 41 ± 8.17 years-old were recruited between June and December 2010. The GINA questionnaire results agreed with the ACQ in 62.5% of cases (controlled 22.5%, partly controlled 12.5%, uncontrolled 27.5% - kappa 0.44, p<0.001), with the ACT in 62.5% of cases (controlled 25.0%, uncontrolled 47.5% - kappa 0.46, p<0.001), with the ADAQ in 45.1% of cases (controlled 26.3%, partly controlled 17.5%, uncontrolled 18.8% - kappa 0.45, p<0.001), and with the RCP in 81.3% of cases (controlled 18.8%, uncontrolled 62.5% - kappa 0.54, p<0.001). Conclusion: Despite the fact that most of these questionnaires have been validated, the agreement between them was moderate. The shortest questionnaire (RCP) showed the highest level of agreement with GINA.

P1297 Factors associated with asthma control in patients with stable asthma

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Introduction: Despite the Global Initiative for Asthma (GINA) guidelines for asthma management, the prevalence of uncontrolled asthma in Greece remains high and factors associated with asthma control unknown. Aim: To predict associated factors with asthma control in stable asthma Methods: 100 Greek patients with stable asthma were included in the study and classified as having controlled (>20) or uncontrolled (<20) asthma by the Asthma Control Test-AST cut-off points. Multiple logistic regression analysis was conducted to identify possible predictors of asthma control. All analyses were conducted with SAS statistical software, version 9.1. Results: Among study participants, those who had follow-up visits solely in emergency were at excess risk of having uncontrolled asthma (OR=3.79; 95% CI=1.21-11.91; p=0.02). Patients with higher levels of MRC were more likely to have their asthma uncontrolled (OR=3.47; 95% CI=1.21-11.91; p=0.02). Patients with higher levels of MRC were more likely to have their asthma uncontrolled by almost 50%. Lastly, no evidence of significant associations with asthma control and physical activity (p=0.47), age (p=0.53), gender (p=0.25), BMI (p=0.60), was noted. Discussion: Greek patients with stable asthma should have regular follow-up visits in order to improve dyspnea and pulmonary function and achieve adequate control and management of asthma.

P1298 Physical, social, and psychological function in asthma patients with and without analgesic tolerance

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Purpose: Ingestion of aspirin and similar drugs triggers severe bronchospasm in some asthmatic patients. The purpose of this study was to compare physical, social
and psychological function between analgesic intolerant and tolerant asthmatic (AIA and ATA, respectively) patients.

Methods: Twenty-seven AIA and 29 ATA patients participated in this study. Respiratory and quadriceps muscle strength (QMS) were measured. Asthma Control Questionnaire and Asthma Knowledge Test were applied. Six-minute walk test was performed, and physical activity level was determined using International Physical Activity Questionnaire (IPAQ). Dyspnea and fatigue perception was evaluated using modified Medical Research Council dyspnea scale and Fatigue Severity Scale, respectively. Psychological function was evaluated using Beck Depression Inventory. Immunology, Genetics and disease specific quality of life were determined using Nottingham Health Profile and Asthma Quality of Life Questionnaire, respectively.

Results: The FEV1, QMS, IPAQ walking score, and Asthma Knowledge Test score were significantly higher in AIA patients as compared to those of ATA patients (p < 0.05). No significant differences were found in asthma control, respiratory muscle strength, symptom perception, six-minute walk test distance, psychological function, and quality of life between the two groups (p > 0.05).

Conclusion: The AIA patients share similar characteristics with ATA patients except better airway function, peripheral muscle strength and physical activity level, and worse asthma knowledge. Presence of analgesic intolerance effects components of physical function in asthma.

P1299

Study of heart rate autonomic modulation in patients with asthma disease

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Background: Evaluate the autonomic activity of patients with asthma in moderate supine and sitting positions.

Material/Methods: Twenty individuals with asthma and 10 healthy individuals had their heart rate and electrocardiographic R-R intervals (iR-R) were recorded for 360 seconds in the supine and seated positions. Heart rate variability was analyzed in the time domain (TM) (RMSD index, i.e., the mean square of the differences between successive iR-R records) and the SDNN index, i.e., the mean standard deviation of normal iR-R in ms) and in the frequency domain (FD), from the low-frequency (LF) and high-frequency (HF) bands in absolute units (au) and normalized units (nu), and the LF/HF ratio.

Results: In TD, the AG showed a significantly higher values for the RMSD and the SDNN in the seated position, compared with the control group (CG). In FD, the AG presented significantly higher values for HF components, in the supine position, and for LF components, and HF in the seated position.

Conclusions: Patients with asthma present reduced HRV when compared with healthy sex- and age-matched controls, with the reduction in sympathetic and vagal activity. Furthermore, both patients and healthy individuals with asthma do not present autonomic adjustments with front postural change. Future studies should examine the HRV as a useful tool to obtain parameters for the stratification of cardiovascular risk in this population, and in the evaluation of different physical therapy interventions designed to treat these patients.

P1300

The health-related quality of life of asthmatic patients according to the illness severity

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Aim: To evaluate the differences in the Health Related Quality of Life (HRQoL) of Asthmatic patients according to the illness severity using the Saint George Respiratory Questionnaire (SGRQ), an specific instrument for respiratory diseases.

Methods: A cross-sectional, descriptive and observational study with 103 outcomes with Asthma (65 women and 38 men) with mean age of 58.48 years (SD 18.30 years) recruited from the Respiratory Service of the University Hospital of Salamanca, Spain from January to July 2010. Socio-demographic and spirometric data (American Thoracic Society criteria) were collected. The HRQoL was evaluated by the SGRQ. Descriptive analysis, one-way analysis of variance and the t-test student were applied using SPSS.

Results: It was found that 30.1% had Intermittent (I), 35% had Moderate Persistent (MP), 25.2% had Moderate Persistent (MOP) and 9.7% had Severe Persistent (SP) asthma according to the Global Initiative of Asthma. The mean of the domains were: Symptoms 39.93 scores (SD 21.83 scores), Activity 43.50 scores (SD 28.10 scores), Impact 24.61 scores (SD 17.81 scores) and the Total 32.84 scores (SD 19.07 scores). There were significant differences (ANOVA) between the groups of severity and the forced expiratory volume in 1 s (FEV1), the Vital Capacity (VC) and all domains and the Total SGRQ. There were no significances in the FEV1, and the VC between I and MP groups (t-test student). Also there was no significations between the three contrast between the MP, MOP and MS groups in all domains and in the total SGRQ.

Conclusions: The HRQoL is related to the asthma severity in this studied sample due to higher differences between the Intermittent Asthma and the other groups.

P1301

Evaluation of lung function and deposition in the nebulization carried by heliox associated with positive end-expiratory pressure in stable asthmatics: Clinical trial

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Introduction: The combination of positive end-expiratory pressure (PEEP) and heliox is an alternative to optimize aerosol.

Background: Assess the influence of nebulization with bronchodilators added by heliox associated with PEEP in lung function and deposition radioaerosol in stable asthmatics during.

Methods: Randomized controlled trial double-blind study involving 32 patients (mean age 47±10 years) divided into four groups: G1: Heliox PEEP + G2-Oxygen + PEEP; G3-Heliox, and G4-Oxygen-submitted to inhalation lung scintigraphy with bronchodilators. Spirometry and cardiopulmonary parameters were evaluated before and after intervention. The deposition index (DPI) was obtained by the ratio of counts in each region of interest (ROI) by the total counts of the right lung and inspiratory capacity (IC) regional obtained by multiplying the total by IC. Statistical analysis used Fisher’s tests, Kruskal-Wallis, Mann-Whitney, Wilcoxon and ANOVA considering p < 0.05.

Results: Post-intervention, the G1 had increased values of predicted FEV1 (p < 0.029) and IC (p < 0.004). In reviewing the DPI the groups, there was a higher DPI in the middle third (44.3%), p = 0.001 and intermediate region (40.2%, p < 0.01). In assessing the DPI between groups, no difference. The IC was higher in regional G1 and G2 (p < 0.05).

Conclusion: The nebulized bronchodilators and heliox combined with PEEP improved lung function. The deposition of drugs was higher in the middle third and intermediate portion of the lungs in all groups. In evaluating the IC regional groups associated with PEEP showed higher values independent of the gas used.

P1302

Effect of nebulization with heliox coupled with positive end-expiratory pressure on the regional chest wall volume variations: A clinical trial

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Positive end-expiratory pressure (PEEP) and heliox are used separately to optimize the nebulization in asthmatic patients. We evaluated the efficacy of nebulizer bronchodilators carried by the heliox coupled to PEEP at the same time, in the distribution of volume variations into the different thoracoabdominal compartments and to correlate them with pulmonary function in stable asthmatic. Randomized controlled trial study involving 27 patients (mean age 46.5±11.67 years) divided into four groups: G1= Heliox PEEP, G2-Oxygen + PEEP, G3-Heliox, and G4-Oxygen-submitted to nebulization with bronchodilators. Spirometry, cardiopulmonary and chest wall volume by Opto-Electronic Plethysmography (OEP) parameters were measured before and after nebulization. For the OEP, 89 markers were attached to the trunk in a sitting position and three measures of slow vital capacity and quiet breathing were captured by six cameras. Statistical analysis used Fisher’s tests, Kruskal-Wallis, Mann-Whitney and Wilcoxon. Post-intervention, regarding to FEV1/FVC ratio, the G1 had increased values when compared to G3 (p=0.02) and G4 compared to G3 (p=0.02). None difference was found in the regional chest wall volume variations between groups and within groups in the initial and end expiratory volume. IC increased in the G1 (0.09L) and G2 (0.08L) when compared to G3 (0.06L) and G4 (0.06L), p < 0.05. There was a correlation between the change in FEV1 and end expiratory abdominal volume (r=0.411, p=0.033). In conclusion, nebulization coupled to PEEP can improve the IC in stable asthmatic patients and pulmonary function without changes the regional chest wall volumes.

P1303

Respiratory movements, chest mobility and sensitivity to pain in patients with sensory hyper reactivity (SHR) asthma and COPD

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Introduction: SHR is characterized of airway symptoms induced by chemicals, scents, cold air and exercise; it affects more than 6% of the Swedish adult population. The symptoms including chest tightness, difficulties to breathe and cough are suggestive for asthma but asthma-tests are negative and asthma medication has no effect.

Aim: To study SHR patients’ respiratory movements, chest mobility, and sensitivity to pain in comparison to patients with asthma, COPD and healthy controls.

241s
Methods: 37 patients with SHR, 32 with asthma, 19 with COPD and 28 controls were included. Chest expansion was measured with a measuring tape, thoracic and abdominal movements were measured with the respiratory movement-measuring instrument (RMMI). Pressure pain threshold (PPT) was assessed at five bilateral points.

Results: The Kruskal Wallis test showed that the groups differed significantly on the subject of lung function, respiratory rate and PPT but also regarding chest expansion and abdominal movements at quiet and deep breathing.

Analyzed with the Mann – Whitney U-test the SHR, asthma and COPD patients had decreased PPT compared to the healthy controls. Compared to the controls and the asthma group the SHR patients had reduced abdominal and thoracic movements. In the COPD group, but not among the asthmatics, abdominal and thoracic movements were reduced compared to the controls.

Conclusion: In SHR respiratory movements and chest mobility are impaired and the patients appeared to have most similarities with the COPD group where 15 out of 19 had severe or very severe COPD. SHR, asthma and COPD patients had all decreased PPT.

P1304
Neurophysiological and functional assessment in patients with difficult asthma control
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Introduction: Asthma usually responds to treatment with inhaled corticosteroids (with or without the addition of long-acting beta agonists or other drugs) and that means the symptoms and normal lung function or as close to normal as possible. Now, when asthma is inadequately controlled despite a therapeutic strategy adapted and tailored to the level of clinical severity, indicated by a specialist and at least six months duration is regarded Difficult Asthma Control (DAC).

Objective: To evaluate the functional and neurophysiological aspects of patients with DAC.

Method: We performed a cross-sectional study in three groups of patients: DACC (making use of oral corticosteroids), DACO (which makes use of smallmuls) and GC (healthy controls of similar age). The evaluation was made by testing six-minute walk. Sit-ups test, static balance with the pressure platform, monosynaptics reflexes (Fenwick and Achilles) and quadriceps strength of the dominant leg.

Results: Asthmatic patients have reduced functional capacity, seen testing the six minute walk test and sit-ups (p <0.05), and patients who use oral corticosteroids showed a reduction in the strength of the quadriceps compared to control (p <0.05).

P1305
Comprehensive spa treatment in the Czech Republic
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Introduction: Patient with asthma (AB) can receive a comprehensive care treatment in specialized centres (Spa’s) in the Czech Republic.

Aim: To evaluate an effect of the comprehensive spa treatment (CST) on ventilatory parameters, chest mobility and posture in children with AB.

Methods: The examined group consisted of 50 medically stable children with AB (aged 11.6±2.5 years) who underwent a 4-week treatment in the Luhacovice Spa. The assessment was performed at baseline and after the treatment and it included lung function tests, maximal inspiratory (MIP) and expiratory (MEP) mouth pressure examination, chest expansion (CE) and kinesiological examination (muscle strength and length). The CST included respiratory physiotherapy, postural exercise and regular physical activity.

Results: Lung function tests showed normal values at the baseline and after treatment. A significant improvement was observed in all ventilatory parameters, respiratory muscle strength and CE at both levels. There was a lower presence of muscle imbalances (shortened and weakened muscles) after the treatment.

<table>
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<tr>
<th>Parameter</th>
<th>Baseline (mean, SD)</th>
<th>After 4-week (mean, SD)</th>
<th>p value</th>
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<tr>
<td>VC (% predicted)</td>
<td>90.9±15.4</td>
<td>97.3±9.3</td>
<td>&lt;0.01</td>
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<tr>
<td>FEV1 (% predicted)</td>
<td>94.7±16.4</td>
<td>104.2±10.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEF (% predicted)</td>
<td>86.4±19.2</td>
<td>97.1±16.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MEF25 (% predicted)</td>
<td>103.5±21.8</td>
<td>117.6±37</td>
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<td>MEF50 (% predicted)</td>
<td>90.3±18.9</td>
<td>100.9±20.3</td>
<td>&lt;0.01</td>
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<tr>
<td>MEF75 (% predicted)</td>
<td>80.2±27.4</td>
<td>97.6±15.8</td>
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<tr>
<td>MEP (cm H2O)</td>
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<td>71.9±28.5</td>
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<tr>
<td>MIP (% predicted)</td>
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<tr>
<td>CE at 4th intercostal</td>
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<td>8.2±2.1</td>
<td>&lt;0.01</td>
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<tr>
<td>CE at sphinctor</td>
<td>4.9±2.1</td>
<td>6.8±1.8</td>
<td>&lt;0.01</td>
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</table>

Conclusion: Children with AB can benefit due to the combination of physiotherapy approaches and physical activity not only in ventilation and breathing mechanism, but also in improved posture.

P1306
State of the respiratory physiotherapy in Spain: Map from online survey results
Daniel Martí¹, Ana Balakal², Elena Gimeno¹, Gerard Muñoz³, Jordi Vilardell³
¹Pneumology Department, Clinic Institute of Thorax, Hospital Clinic-IDIBAPS, Barcelona, Spain; ²Pneumology Department, Hospital del Mar: Parc de Salut Mar-IMIM-CIBERESP, Barcelona, Spain; ³CERAL-CIBERESP, Centre de Referència de l’Hospital del Mar-IMIM, Barcelona, Spain

Objective: To define the map of respiratory physiotherapy (RP) in Spain.

Design: Online questionnaire.

Setting: A 39 items online survey was allocated in a survey web during 4 months.

Direct contacts, professional colleges, physiotherapy services, universities and professional associations were invited to answer once every professional. The survey was about clinical, teaching and research profile questions and even it was posted on a web-side respiratory national society during the same period.

PARTICIPANTS: graduated physiotherapists living and working in Spain.

Results: 818 questionnaires were answered. The answers obtained had a heterogeneous territorial distribution; Galicia, Catalunya and Castilla- la Mancha were the most responder areas. 560 physiotherapists (69%) performed regular RP treatments. 123 (15%) were involved in respiratory research and 137 (17%) in RP teaching at the university or in post-graduate courses. However, RP was not homogeneously established over the country and only 21.5% of the physiotherapists were fully involved in RP. Physiotherapists involved in RP worked in private centres (25.2%) and at public hospitals (20.5%). Only 309 of the total (38%) obtained a RP post-graduate specialisation in respiratory physiotherapy.

Conclusions: The response rate allows to define the professional situation of RP across Spain. Our specialisation is not well established and its distribution is not homogeneous over the country. There is a need to increase the number of RP post-graduate trained professionals and researchers in order to improve the quality of Respiratory Physiotherapy over Spain.

P1307
OSCE as an evaluation method for graduate students in respiratory therapy
Cibele C.B. Marques da Silva, Adriana C. Lunardi, Felipe A.R. Mendes, Flavia Ferreira, Celsio R.F. Carvalho. Physical Therapy, School of Medicine of University of Sao Paulo, Sao Paulo, Brazil

Objective: The aims of this study were to assess the use of OSCE (objective structured clinical evaluation) as a tool to evaluate the abilities of graduate students in respiratory therapy and to verify the internal consistency of this exam.

Methods: Forty seven students were evaluated by two exams: traditional and OSCE. Each question (traditional) or station (OSCE) ranged from 0.0 to 2.0 and the total score of both exams was 10.0. The exams were prepared by independent educators that were blinded to the final grades. Internal consistency of OSCE stations was assessed by four experienced Respiratory Therapists.

Analysis: Internal consistency was tested by Cronbach’s Alpha. The relation between scores obtained in both exams was analyzed by Iland Altman and Pearson’s test.

Results: The average score of the students’ grades ranged from 4.5 to 9.1. The internal consistency of OSCE stations was considered good (0.7). The agreement between exams was estimated and it was observed that they are not comparable. It was also observed a low agreement between both exams (r=0.1; p=0.9; Pearson correlation). The correlation between two exams was moderate.

Conclusions: Our results showed that OSCE and traditional exams are not related. The OSCE exam had good internal consistency and assessed distincts aspects of traditional exam.

P1308
Management of dysfunctional breathlessness (DBY) – A retrospective service evaluation
Ashay Dwarkanath, Vera Davidson, Claire Taylor, Anthony Fennerty. Respiratory Medicine, Harrogate and District NHS Foundation Trust, Harrogate, Yorkshire, United Kingdom

Introduction: DBY has an incidence of about 10% and may pose a diagnostic and therapeutic challenge. We have established a physiotherapist run clinic to manage this condition.

Aim: To evaluate the outcome of a physiotherapist run DBY clinic.

Method: The diagnosis of DBY was made on the basis of exclusion with a normal clinical examination,lung function and echocardiogram,or with symptoms disproportionate to measurements of severity of their respiratory illness. Patients were assessed by the physiotherapist with regard to their breathing pattern and the Nijmegen (Ni) score,with a score over 23 being regarded as diagnostic of DBY. Consecutive patients referred to the clinic over 24 months were reviewed. The following parameters were analysed-underlying respiratory illness,breathing pattern,Ni score (Pre and Post Intervention),HAD scores and the intervention modalities.

Results: 51 patients (males-20) were referred to the clinic in 24 months. The mean age was 60.2 range, 20-84.26/51 patients had chronic cardiac respiratory illness.28/51 patients had an abnormal breathing pattern.
37 patients had a pre intervention Ni score over 23 (mean-29, range, 23-42). Interventions included patient education, cognitive behaviour therapy, breathing exercises and training. Post intervention the Ni score fell below the diagnostic threshold in 29/37 patients (mean reduction-14, range, 3-22). HAD scores was used to assess the degree of mood impairment and there was no linear correlation with the pre intervention Ni score.

Conclusion: A clinically significant improvement in symptoms as measured by the Ni score was achieved in 78% of the patients referred to our DYG clinic. There was poor correlation between HAD score and the Ni score.

P1309
Clinical outcomes of spinal cord stimulation (SCS) to restore cough
Anthony DiMarco1, Krzysztof Kowalski1, Robert Geertman3, Dana Hromyak4, Frederick Frost1, Gregory Nemunaitis1. 1Department of Physical Medicine and Rehabilitation, Case Western Reserve University and MetroHealth Medical Center, Cleveland, OH, United States; 2Department of Medicine, Case Western Reserve University and MetroHealth Medical Center, Cleveland, OH, United States; 3Department of Research, Case Western Reserve University, Cleveland, OH, United States

Background: In spinal cord injury (SCI), paralysis of the expiratory muscles often results in an ineffective cough and consequent inability to effectively clear airway secretions. SCS is an effective method of expiratory muscle activation.

Design: Clinical trial assessing the clinical outcomes and side effects of SCS to restore an effective cough in 12 SCI subjects.

Main outcome measure(s): Ease in raising secretions, requirement for trained caregiver support for secretion management and incidence of acute respiratory tract infections.

Results: Based upon questionnaire responses, the degree of difficulty in raising secretions improved markedly, and the need for alternative methods of secretion management lung function was observed in FVC: 3.6±0.9 vs 4.0±1.0 L, FEV1:3.0±0.7 vs 3.4±0.8 L, FEF25-75%: 3.4±0.8 vs 8.3±0.9 L/s, ERV: 0.35±0.4 to 0.66±0.4 L/min and MVV:103.4±22 vs 137.3±29 L/min, all to p<0.001 compared to pre-operative phase. We found an increase of 0.06 l in the FVC and 5.9 l/min in the MVV after SCS for each 1 cm of neck circumference decrease. For each 1kg/m² lost after the SCS FVC increase 0.03 l and MVV 2.74 l/min.

Conclusion: The loss of weight induced by BS provides an increase in the lung function and the reduction of fat around the neck appear to be more important to increase lung function than BMI. Financial support: CNPq-Brasil.

P1310
Influence of the loss of weight after bariatric surgery in the respiratory muscle endurance

Background: Weight loss induced by bariatric surgery (BS) in morbidly obese has effects on respiratory function, however the relationship between weight loss and respiratory muscle endurance is unknown.

Objective: To study relationship between weight loss and respiratory muscle endurance induced by BS.

Methods: We evaluated anthropometric parameters (waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR), neck circumference (NC) and lung function tests (spirometry and respiratory muscle strength and maximal voluntary ventilation)) in 39 patients (29 F), mean age 35.9±10.9 years, without respiratory or heart diseases, before and after gastric bypass, Roux-en-Y surgery.

Results: After 10.8±7.7 months of BS we observed a decreasing in the anthropometric values (p<0.05) of weight:124.8±17.5 to 88.8±14.28 kg, BMI: 47.9±5.6 to 34.3±4.75 kg/m² and NC:43.5±3.9 to 37.2±4.7 cm. Significantly improved lung function was observed in FVC: 3.6±0.9 vs 4.0±1.0 L, FEV1:3.0±0.7 vs 3.4±0.8 L, FEF25-75%: 3.4±0.8 vs 8.3±0.9 L/s, ERV: 0.35±0.4 to 0.66±0.4 L/min and MVV:103.4±22 vs 137.3±29 L/min, all to p<0.001 compared to pre-operative phase. We found an increase of 0.06 l in the FVC and 5.9 l/min in the MVV after BS for each 1 cm of neck circumference decrease. For each 1kg/m² lost after the BS FVC increase 0.03 l and MVV 2.74 l/min.

Conclusion: The loss of weight induced by BS provides an increase in the lung function and the reduction of fat around the neck appear to be more important to increase lung function than BMI. Financial support: CNPq-Brasil.

P1311
Airway clearance techniques (ACT): A retrospective study in 188 patients, 96 of which with respiratory failure (RF)
Francesco Di Abensca1, Barbara Garabelli1, Lorenzo Appendini1, Gloria Savio1, Agnese Barison1, Nadia Baschini1, Paola Baraldi1, Bruno Banfi1. 1Divisione di Pneumologia Biabilitativa, IRCCS Fondazione Salvatore Maugeri, Veruno, Novara, Italy; 2Department of Statistics, Consorzio Valutazioni Biologiche Farmacocinetiche, Pavia, Italy

ACT comprise PEP-Mask and ELTGOL (PE) commonly used in our clinical practice and a recently introduced device, Temporary PEP (T-PEP®, UNIKO®).

The aim of this observational retrospective study was to compare the efficacy of T-PEP group on possible effects and specific indications of T-PEP compared with PE. We re-evaluated data from 188 patients (113 males, mean 70±10 years) including 96 patients with RF (i.e. in LTOT and/or mechanical ventilation, MV), 97 COPD and 75 COPD and/or bronchectasis patients, with or without exacerbation consecutively treated with ACT. 55 subjects were treated with T-PEP, 133 with PE. Demographic, clinical and physiological characteristics between ACT groups were similar. Repeated measures analysis of variance were used. After ACT, significant improvements in all physiological measures were found with no difference between groups: p<0.001 for FVC, FEV1, PEF, SaO2, PaO2, PaCO2/FiO2. Patients on LTOT showed that the need for O2 therapy decreased after ACT in T-PEP group (1.56±1.301 to 1.46±1.01 L/min – FiO2 0.245±0.048 to 0.260±0.041%) whereas increased in PE group (0.99±0.809 to 1.49±1.16 L/min – FiO2 0.242±0.028 to 0.273±0.088% p<0.029). Among patients not on MV, T-PEP group showed a trend to an increase of PaO2/FiO2 (p=0.078). ACT can improve physiological parameters with no difference between T-PEP and PE. In the T-PEP group, the reduction on needs of O2 therapy in LTOT patients and the trend of an increase of PaO2/FiO2 in patients not in MV seem to indicate that further studies are needed to target differently ACT in patients with RF Supported in part by MPR, Italy.

P1313
Change in erythrocyte aggregation during phototherapy in patients with COPD
Yulduzkhon Kayumova, Nigora Mukhiddinova. Ministry of Health of the Republic of Uzbekistan, Republican Specialized Scientific-Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan

Introduction: Aggregation of red blood cells affects the efficiency of blood flow and oxygen delivery to tissues. This determines the importance of studying this parameter in patients with COPD and to seek correction in case of violations.

Aim: To study erythrocyte aggregation in patients with COPD during phototherapy with lamps with ceramic coating.

Methods: We studied 30 patients in stable phase of COPD (22 men and 8 women) aged 39-64 years, divided into 2 equal groups: 1st - after phototherapy for 10 days, 2nd - without phototherapy. Control group - 10 healthy men aged 40-58 years. Phototherapy was held with infrared light from ceramic-coated lamps of series KL, ZB and GI with wavelengths of 2-40 microns. Spontaneous aggregation of erythrocytes of venous blood was quantitatively evaluated by a special system of criteria for microphotographs of aggregates: the 1st group - before and after 10 days of phototherapy, while the 2nd and control groups - once.

Results: In the 1st group before the start of phototherapy erythrocyte aggregation...
The mean Modified Borg Scale was reduced from 2.88 to 2.02 (p < 0.05) showing that the number of emergency department attendance was reduced by 44.5% from 1.91 to 1.06 (p < 0.001) respectively. Together with a small increase in the use of propofol we observed a substantial reduction in the use of midazolam and morphine.

**References:**

**Conclusion:**
Chronic Obstructive Pulmonary Disease (COPD) was ranked second among common respiratory diseases in Hong Kong. A pilot of Respiratory Nurse Clinic for COPD has been implemented since December 2009 in United Christian Hospital, Hong Kong, China. The Respiratory Nurse Clinic for COPD was run by qualified Respiratory Nurses and accredited locally since December 2009. Confirmed COPD patients who were high risk of hospitalization could be recruited. The key components of the program included patient registry, risk stratification, different models/levels of care with holistic approach, home non-invasive ventilator program, patient empowerment program and 24-hours hotline service.

**Results:**
The first 100 COPD patients were analyzed for their healthcare utilization for three months before and after joining the clinic. Their mean age was 74.6 ± 12.0 years (n = 100). The eclectic world of respiratory nursing

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**P1314**
Can education and electronic prescription improve the use oxygen in acute clinical settings?

Gareth Ebbon, Ajit Thomas, Shiva Bikmalla, Asad Ali, Vikas Panamiyi, Ben Beauchamp, Rahul Mukherjee. Department of Respiratory Medicine & Physiology, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

**Introduction:** Recent data on effects of hyperoxia in patients with coronary artery disease, brain injury [1] and post resuscitation patients [2] have shown increased mortality and morbidity. This calls for efforts to reduce unnecessary oxygen use in hospitals, which we instituted via targeted multidisciplinary education and widening the use of electronic prescription of oxygen between 2008 and 2010.

**Method:** Cross-sectional point prevalence of oxygen prescribing practice was audited at out patient hospital in November 2008 and November 2010 excluding Intensive care, paediatric and maternity wards. Between the 2 oxygen audits, we widened and improved electronic prescribing with a multidisciplinary training program on oxygen use for all caregivers.

**Results:** At the Nov 2010 point of data collection, 185/1267 (15%) patients were on oxygen. Of these a clear valid oxygen prescription was noted in 149 (81%); 46% of saturations documented were within target range. The proportion of patients in hospital receiving oxygen had reduced from 28% (191/666) since 2008; the prescription rate improved from 57% to 81%.

**Conclusion:** With the focus on education, increased awareness through local and national alerts and electronic prescriptions of oxygen, we have noted almost halving of in-hospital oxygen use and higher rates of oxygen prescription. There is however room for improvement in adherence to target saturation oxygenation.

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**P1315**
Manage growing demand: Respiratory nurse clinic keeps people with COPD healthy

Shu Wah Steve Ng, Wai Yee Tsang, Chung Leung Penny, Lee Veronica Chan, Chung Ming Chu. Medicine & Geriatrics, United Christian Hospital, Hong Kong, China

**Introduction:** Chronic Obstructive Pulmonary Disease (COPD) was ranked second as a respiratory cause of hospitalization (14.6%) and inpatient bed-days (20.5%) among common respiratory diseases in Hong Kong. A pilot of Respiratory Nurse Clinic for COPD has been implemented since December 2009 in United Christian Hospital in Hong Kong. It focused on reducing the need for intensive medical care for COPD patients. This preliminary review aims to evaluate the effectiveness of the clinic.

**Methodology:** The Respiratory Nurse Clinic for COPD was run by qualified Respiratory Nurses and accredited locally since December 2009. Confirmed COPD patients who were high risk of hospitalization could be recruited. The key components of the program included patient registry, risk stratification, different models/levels of care with holistic approach, home non-invasive ventilator program, patient empowerment program and 24-hours hotline service.

**Results:** The first 100 COPD patients were analyzed for their healthcare utilization for three months before and after joining the clinic. Their mean age was 74.6 ± 12.0 years (n = 100). The mean Modified Borg Scale was reduced from 2.88 to 2.02 (p < 0.05). It is by 16.4% less than in the 2nd group, where the index was 8.5 ± 1.3. It is by 15.4% more than in the 3rd group, where the mean was 5.5 ± 1.3. But after testing the differences between all 3 groups, a statistically significant difference (p < 0.05) was detected only between the 2nd and control groups.

**Conclusion:** Erythrocyte aggregation increases in patients with COPD. During the 10-day course of treatment with infrared light from lamps with ceramic coating this indicator tended to normalize.

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**P1316**
Practical nursing strategies in the management of pemphigus patients

Lynda Holsworth1, Trudi Miller1, Brownyn Levey1, Julian Goss1, Sanjiv Manjra2, Devika Williams1, 2, Glen Westall1, 2, Gregory Snell1, 2. Allergy, Immunology & Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, Australia; 2Cardiothoracic Surgery, The Alfred Hospital, Melbourne, Victoria, Australia

**Background:** In severe emphysema hyperinflation results in reduced quality of life and reduced exercise capacity. Portaero Inc. has developed a technique to create a permanent incision passage from the parenchyma of the lung through the chest wall (pneumostoma) to enable trapped air to vent. A pilot study demonstrated that the creation of a pneumostoma was feasible, safe and potentially beneficial to patients with severe emphysema.

**Objectives:** This report describes the nursing strategies developed in association with this novel device.

**Methods:** Pneumostomomas were created in a series of 8 patients. Tracts were created via a percutaneous incision and placement of an access tube which remained in place for 3-4 weeks. The pneumostomomas were maintained by a disposable tube changed daily by the patient.

**Results:** Early post operative complications included subcutaneous emphysema (8) and wound infection (1). Identified long term issues were problems with skin integrity (4), superficial granulation tissue (3), recurrent localised infection (2), bleeding and pain within the tract following activity (2). Inserting the daily tube was complicated by angulation and collapsibility of the tract, resistance entering between the ribs and anxiety. These problems were addressed with careful attention to skin integrity, treatment of granulation tissue with topical steroids and medical management of pain and infection. A bronchoscope was used to visualise the tracts, assess patency and identify tract direction or narrowing.

**Conclusion:** Continuous education and close support from nursing staff while the patients learned to deal with these issues enabled 6 of the patients to maintain a pneumostoma long term (between 6 and 18 months).

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**P1317**
Daily weanscreen in mechanically ventilated patients: effects on sedation, analgesics and duration

J. van Rosmalen, F. van Beers, A. van Hees, P. Vos, P. van Berkom, J.A.H. van Oers. ICU, St Elisabeth Hospital, Tilburg, Netherlands

**Introduction:** The duration of mechanical ventilation (MV-duration) should be limited as much as possible to avoid complications.

**Objective:** The aim of the study was to find out the impact of a daily weanscreen on MV-duration.

**Setting:** A 20-bed mixed medical–(neuro-)surgical Intensive Care Unit.

**Methods:** In 2009 the sedation protocol was prescribed each day by the intensivist. In 2010 we introduced a 4 interventions weanscreenprotocol, including: Daily Spontaneous Awakening Trial (SAT), Rapid Shallow Breathing Index (RSBI), Spontaneous Breathing Trial (SBT) and MD enumerates reason to continue. From January to December 2010 we assessed all ventilated patients every day from Monday to Friday. The subsequent 4 steps of the weanscreen protocol were carried out by a ventilation practitioner (R.N.) to promote extubation. The amount of sedatives per year was divided by the number of ventilated patients, resulting in an average dose midazolam/propofol/morphine per patient. The MV-duration was evaluated and compared with 2009.

**Results:** The 672 patients in 2010 were compared to 594 patients in 2009. SAPSII was the same in both cohorts, Median MV-duration decreased from 42 to 38 hours (p < 0.001). Midazolam (mg/patient) was at 257 ± 393 mg/patient in 2009 and 262 ± 279 mg/patient in 2010. Morphine (mg/patient) was at 251 ± 200 mg/patient in 2009 and 251 ± 200 mg/patient in 2010. Conclusions: In our population we succeeded in reducing the use of midazolam and morphine by a daily 4 component–weanscreen, and a 10% decrease in MV-duration (statistically n.s.).

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**P1318**
Home non-invasive ventilation service for patients with chronic respiratory failure

Shu Wah Steve Ng, Wai Yee Tsang, Yuen Yee Anna Chan, Lee Veronica Chan, Chung Ming Chu. Medicine & Geriatrics, United Christian Hospital, Authority Hospital of Hong Kong, Hong Kong, China

**Introduction:** There is increasing use of Non-Invasive Ventilation (NIV) in the management of patients with chronic respiratory failure such as Chronic Obstructive Pulmonary Disease (COPD). It was estimated that patients requiring home mechanical ventilation was 2.9 per 100,000 populations in 2004 in Hong Kong.
Most of them (94.8%) were treated by NIV. The domiciliary NIV program has been established in a local acute hospital to provide optimal and comprehensive care for the patients since 2004. Methodologies: The service was run by qualified Respiratory Nurses. The enhancement program has provided more structured, proactive and specialized NIV service. The key components of the service include patient registry, primary nurse model, clinical pathway, patient and carer empowerment, nurse clinic, quality assurance and 24-hours hotline. Results: There were 145 patients recruited since 2005. The gender ratio was about 4 to 1 (117.5% of male and 28, 19.3% of female) with mean age of 71.98±8.91. After receiving domiciliary NIV service, their attendance numbers in emergency department, unplanned admission and length of stay were significantly reduced. Conclusions: The domiciliary NIV service could provide holistic, continuous and cost-effective care for these high-risk patients with complex needs. It could reduce avoidable healthcare utilization of these patients.

PJ1319
Concept of caring – Family caregiver’s perspective on end-of-life care in advanced COPD
Betina Korn. Department of Respiratory Medicine, St. James’s Hospital, Dublin, Ireland

Background: Informal family caregivers provide the majority of care to patients with advanced COPD wishing to be cared for and die at home. Little is known about family caregiver’s perspective on end-of-life care.

Aims: This study aimed to conceptualise caregiver’s insight into caring for their family member with advanced COPD.

Methods: This sub analysis of data was part of a larger study and utilised an explorative descriptive qualitative design. Eight family caregivers that had cared for a loved one dying at home from COPD committed to semi-structured interviews about their experience. Transcripts of the interviews, field notes and reflective journal entries underwent a qualitative template analysis.

Results: The concept of “caring” was one of five themes identified. Seven subthemes within this theme describe the level of involvement caregivers had in the care of their family member. Carers understood complex care issues, describe the effect caring has on their own life and demonstrate organisational skills. They describe how family and kinship enables them to care and how they witness, recognise and respond to physical decline and suffering of their dying family members. Caring for their loved one was an all-encompassing, all-consuming affair and left them exhausted but gratified. A novel finding was the caregiver’s detailed knowledge about their experience. Transcripts of the interviews, field notes and reflective journal entries underwent a qualitative template analysis.

Conclusions: The key finding was family caregiver’s experiential knowledge. This knowledge is largely unrecognised by health care professionals. It remains a challenge to health care professionals to tap into this wealth of caregiver’s experiential knowledge in order to provide better end-of-life care in advanced COPD.

P1320
Clinical effectiveness of manual hyperinflation on atelectasis in patients with acute respiratory failure
Li Hsiang Yang1, Suh-Hwa Maa 2. 1Department of Nursing, Chang Gung Memorial Hospital, Taoyuan, Taiwan; 2Department of Somatics and Sports Leisure Industry, National Taitung University, Taitung, Taiwan

The literature and the clinical experience all demonstrate that manual hyperinflation (MH) in patients receiving mechanical ventilation may improve sputum clearance and ventilation. The purpose of this study was to examine the effectiveness of MH in patients with lung atelectasis associated with ventilation support. Twenty-eight patients with lung atelectasis associated with ventilation support, and stable vital signs were randomized into either an experimental group (n=14), or a control group (n=14) in the pulmonary intensive care unit of a Medical Center in northern Taiwan. The MH technique was carried out at a rate of 8–13 breaths per minute for a period of 20 minutes each session, 3 times per day until weaned from the ventilator. The control group received standard prescribed mechanical ventilation without supplemental MH. Sputum contents (wet/dry weight ratio, viscosity), respiratory system capacity (spontaneous tidal volume (VT), maximal (Pt-max.), index of rapid shallow breathing (IVT), dynamic lung compliance, chest x-ray signs and oxygenation ratio (PaO2/FiO2) were all measured just prior to the MH on Day 0 as baseline, and then each day for the next three days. The results showed significant improvements in the scores of the experimental group compared to those of the control group for sputum viscosity (p=0.011) and the index of rapid shallow breathing (p=0.008) after adjusting for covariates. Other outcome variables did not differ significantly between the experimental group and the control group.

Abstract P1322 – Table 1. Summary of findings

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<th>Oncology/Rheumatology</th>
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<td>Comfort (scale of 1–10; 1=uncomfortable, 10=comfortable)</td>
<td>Mean 5, Mode 5, Median 5</td>
<td>Mean 7, Mode 7, Median 8</td>
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<tr>
<td>Nurses with post registration training in ICD management</td>
<td>18%</td>
<td>43%</td>
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<tr>
<td>Nursing staff who think they have adequate training (pre &amp; post registration)</td>
<td>17%</td>
<td>29%</td>
</tr>
<tr>
<td>Use dedicated chest drain observation chart on ward</td>
<td>24%</td>
<td>100%</td>
</tr>
<tr>
<td>Aware of observations to be recorded for ICD’s (volume, swelling, bubbling – if applicable)</td>
<td>69%</td>
<td>100%</td>
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<tr>
<td>Aware of recommended volume of drainage in 1st hour (1–1.5 litres)</td>
<td>39%</td>
<td>57%</td>
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P1321
Persistent symptoms of hospitalized COPD patients in the palliative phase
C.M. van Otteren, W.J.C. van Heusden. Pulmonary Department, Medisch Spectrum Twente, Enschede, Netherlands

Introduction: Literature shows that COPD will be the third cause of death worldwide and will lead to increasing health costs. Over time a great amount of severe COPD patients will demand different treatment and counseling with special attention for palliative care. Recently a new guideline has been developed in the Netherlands describing the palliative care for COPD patients. This guideline promotes more attention for quality of life, symptom control and psychosocial support. The first step in improving palliative care is measuring patient’s symptoms and impairments.

Aim: The aim of this study was to measure the incidence of persistent symptoms, fear and depression in admitted COPD patients in the palliative phase.

Results: 210 COPD patients in the palliative phase admitted to hospital with a COPD exacerbation were included. On day three the CCQ and HADS questionnaires were recorded. The rate of dyspnea, fatigue, fear and depression were scored on day 1 and 7 by means of VAS score (0-10).

Results: The median HADS score fear was 9.5 (1-19), depression was 7 (4-15). The median VAS score dyspnea day 1 was 3 (3-10), day 7 was 5 (1-9). The median VAS score fatigue day 1 was 7 (3-9), day 7 was 4.5 (1-10). The median VAS score fear day 1 was 3.5 (0-10), day 7 was 2 (0-10). The median VAS score depression day 1 was 5 (0-10), day 7 was 3 (0-10).

Conclusion: Fear and depression scores are high among patients with COPD in the palliative phase at admission in hospital and improve only partly during treatment of the exacerbation. There is no improvement in dyspnea score during admission.

P1322
A survey of nursing staff on intercostal drain (ICD) care in a tertiary centre
R. Nasser, R. Ahmed, A. Scott, M.E.J. Callister. Respiratory Medicine, St. James’s University Hospital, Leeds, West Yorkshire, United Kingdom

Introduction: A recent audit of ICD’s for pleural effusions in our 800 bedded tertiary centre revealed that in a 2 month period a significant proportion of drains were being managed on non respiratory wards (44% oncology & 16% other medical wards). Guidelines recommend that ICD’s are nursed on wards familiar with drains and their management.

Method: We carried out an anonymous survey of nursing staff to enquire about training, knowledge & comfort in managing ICD’s. The completed survey questionnaires were returned via internal mail.

Results: 110 questionnaires were distributed & 71 were returned (65%). 76% were Staff nurses, 22.5% Sisters & 1.5% were matrons. 77% had been qualified more than 3 years. 38% worked in general medicine, 20% in respiratory, 24% in Oncology & 18% in other specialties. A majority of the nurses felt they did not have adequate training, very few of them had any post registration training.

Conclusion: There is a clear need for education and training for nursing staff who are expected to look after patients with ICD’s. There is also a need for a trust wide chest drain observation chart.

P1324
Evaluation of health quality of patients with asthma and chronic obstructive pulmonary disease
Katarzyna Kiecicka, Anna Doboszyńska. Clinical Nursing Department, Medical University of Warsaw, Warsaw, Poland

Background: Bronchial asthma and chronic obstructive pulmonary disease (COPD) are characterized by inflammatory process in the airways, leading ultimately to their obstruction. Complex view on these diseases is associated with patients’ quality of life. Therefore, evaluation of the quality of life is of utmost importance, especially in the complex assessment of therapeutical process.

Objectives: This study aimed at evaluating and comparing life quality in two groups of patients, degree of dyspnea, and level of illness acceptance.

Aim: The study involved 100 patients with diagnosed bronchial asthma or COPD. Mean age of patients was 63 years. Investigative material was obtained with diagnostic poll with the aid of questionnaires based on: Saint George’s Respiratory Questionnaire, Medical Research Council dyspnea scale and Acceptance of Illness Scale. Collected data were analyzed statistically.
Results: In the group of asthmatic patients, total score of SGRQ was 54.9 ± 6.7 and was significantly lower than that in the group of patients with COPD - 67.9 ± p=0.0001. Strong negative correlation of life quality with illness acceptance was shown in both asthmatic and patients with COPD (R=-0.96, R=-0.98; p<0.001). Statistically significant relationship between respondents’ life quality and severity of dyspnea (F=11.71; t=0.83; p<0.000001).

Conclusion: 1. Statistically significantly lower quality of life is seen in patients with COPD in comparison with asthmatic patients. 2. Quality of life is worsening with more severe or uncontrolled disease. 3. Quality of life of examined patients is closely correlated with level of illness acceptance.

P1325
Nurse care for patients with chest drainage and creation of local procedural standards
Renata Sabo, Zuzana Taligov, Jan Platino, David Magula, Dalibor Petras.
2nd Pneumology, Specialized Hospital of St. Svoradus, Nitra, Slovakia (Slovak Republic)

Introduction: Drain is simple or complicated device or entire system, which serves to evacuate unwanted secretions or air from the pleural space. Today, the chest drainage (CD) is frequently used in pneumology. Its application is pathophysiological favourable, because the accumulation of fluid/air in body cavities prevents oxygenation of the cells, slows down mobilisation of collagen, prevents lymphatic drainage and creates a bounded space, resulting to delay the healing process.

Aims: Upon nurse assistance during CD to share own experience with formation of the local procedural standards.

Methods: From 2007 to 2009 CD was performed on 159 patients (pts). Empyema had 88 pts, malignant pleural effusion 58 pts and pneumothorax 13 pts.

Results: CD was without complications in 134 pts (84.3%). The complications occurred in 31 pts (19.5%). In 7 pts (4.4%) occurred trapped lungs; pain occurred in 31 pts (19.5%). In 7 pts (4.4%) collapse during CD was without complications in 134 pts (84.3%). The complications had 88 pts, malignant pleural effusion 58 pts and pneumothorax 13 pts.

Introduction: Upon nurse assistance during CD to share own experience with formation of the local procedural standards.

P1326
Obesity hyperventilation syndrome in the health area of the public company hospital Costa del Sol: Why do women have a higher prevalence? Juan Antonio Piña Fernández1, Ana Mochón Doña1, Juan Jose Santos Gonzalez2, Mar Sánchez Jimenez2, Pilar Fuentes Gala2, José Joaquin Cebrian Gallardo2, Luis Fernandez de Rota2, Francisco Linde de Luna2, Alicia Padilla Galo2, Ana Escobar Dueñas2, Pilar Cuellar2, 1VitalAire, Neumology, Empresa Publica Hospitalica Costa del Sol, Marbella, Malaga, Spain; 2Neumology, Empresa Publica Hospitalica Costa del Sol, Marbella, Malaga, Spain

Introduction: After detecting in a previous study on the prevalence of obesity hyperventilation syndrome (OHS) in the health area of the public company Hospital costa del sol that the prevalence of OHS in women was almost twice the rate of men (men 22.2%, women 56.81%), we try to find out what could be the factor or factors that determine these results.


Results: We analyzed 51 patients. Sex: Male (15), Women (36).

Phase 1: Underpinning theories. 1) The newly developed theory of CARe emphasizes the need for solution-focused nursing integrating a double goal: patient wellbeing and treatment efficacy. According to CARe, patients expect to be actively involved in the ongoing adjustment of the NIV treatment integrating their personal habits, preferences and expectations aiming at maximizing their overall wellbeing. 2) Experimental learning is learner-centred focusing on practical experience and learning by doing. Phase 2: Modelling the intervention. Skills of involvement, emotional attunement and monitoring NIV are central components of the intervention model. The teaching method is high-fidelity simulation. To evaluate learning outcome within the tree component areas we will use the Model of Practical Skill Performance.

Conclusion: We expect the learning outcome will be beneficial to both patients and nurses. The educational intervention is ready to test for feasibility.

P1329
A phenomenological study of pain in patients suffering from COPD
Marie Hustavenes1, Elise Austegaard1, Dagfinn Nåden2, Randi Andenæs2, 1Department of Medicine, Levienberg Diakonale Hospital, Oslo, Norway; 2Anaesthetic Ward, Randers Regional Hospital, Randers, Denmark

Introduction: Taking care of COPD patients in non-invasive ventilation (NIV) requires Complex Adaptiveness (CARe) from the involved nurses. Nurses are struggling to manage NIV and providing high quality nursing care for these patients requires plenty of practice.

Aim: To develop an intervention through high-fidelity simulation as a tool for less experienced nurses to advance their skills in providing NIV nursing care.

Method: We used the first two phases of the Medical Research Council framework. Firstly, in the preclinical phase we evolved the underpinning theories of the intervention. Secondly, in the modelling phase we identified the components of the intervention.

Results: Phase 1: Underpinning theories. 1) The life changiing pain, 2) the pain of dyspnoea attacks, and 3) the non-communicated pain.

Conclusion: Patients described various appearances of pain. Three major essences were identified: 1) The life changing pain, 2) the pain of dyspnoea attacks, and 3) the non-communicated pain. Regarding the first essence, pain was described as life changing since it implied a dramatic limitation on their lived life and the painful knowledge of progression. Concerning the second essence, dyspnoea attacks were experienced as physical pain in chest, head and muscles, as well as pain of acute fear of dying due to lack of air. Relating to the third essence, pain was not communicated to health care personnel due to lack of time, fear of not being taken seriously, or that they were never asked. Pain became private, and various methods of relieving pain were sought elsewhere.

Conclusions: Patients with severe COPD experienced pain at a level that interfered with their daily life, which had a negative impact on their quality of life.
1330
Caring for a family member with COPD: Exploring carers’ needs
Raquel Gabriel1, Cristina Jácome1, Daniela Figueredo1,2, Alda Marques1.
1School of Health Sciences, University of Aveiro, Aveiro, Portugal; 2Member of
the Research Unit UniFAI (Unidade de Investigação e Formação Sobre Adultos e
Idosos), University of Porto, Porto, Portugal.

Background: Research of the impact of Chronic Obstructive Pulmonary Disease
(COPD) on patients’ family carers is limited when compared to other chronic
diseases such as cancer, heart disease or dementia. The disease places a particular
burden on families but their support is crucial for the patient’s adjustment to the
disease. However, current knowledge on the specific needs of family carers living
with a patient with COPD is scarce.

Aims: This exploratory study aimed to contribute to a better understanding of the
family carers’ needs of patients with advanced COPD (stage III and IV).

Methods: Qualitative semi-structured interviews were conducted with ten carers
(females=8), with a mean age of 57.6 (SD=7.1) years old. The majority were spouses
(n=9) and were caring for more than 4 years (n=6). All interviews were
audio-recorded, transcribed and submitted to thematic analysis.

Results: Main results suggest carers’ needs for: i) information about the disease
To provide adequate care and to discern between kinds of attention needed to respond
to symptoms (e.g., difficulties in recognising when a exacerbation is occurring)
(n=8); ii) emotional support, like having someone trustworthy to talk about the
caregiving experience (n=4); iii) respite care, in order to allow carers to take some
time for their own (n=3); iv) instrumental support, as male carers reported
difficulties in providing housework or meal preparation (n=2).

Conclusions: The findings suggest that patients with COPD have significant
Concerns and fears about the irreversible process of their disease. Adequate knowl-
edge about these aspects will allow health professionals to adjust pulmonary
rehabilitation programs in the context of COPD. Understanding family needs pro-
ciding carers with education about the disease and emotional support is essential to the
management of COPD and to support carers in their caregiving role.

1331
Living with COPD: A perspective on patients’ concerns
Cristina Jácome, Raquel Gabriel, Alda Marques, Daniela Figueredo. School of Health
Sciences, University of Aveiro, Aveiro, Portugal.

Background: The World Health Organization has emphasized the need for a
patient-centred health care for the management of chronic conditions. COPD is a
highly incapacitating chronic disease and its non-pharmacological management has
been based on pulmonary rehabilitation programs. However, patients’ perspectives
regarding their own concerns have received little attention from these programs,
which is crucial to design adequate patient-centred interventions.

Aims: The aim of this study was to identify the specific concerns and fears of patients
with moderate-to-severe COPD, regarding their actual and future condition.

Methods: A qualitative, cross-sectional study was carried out with 18 COPD
outpatients. Data were collected using audiotaped semi-structured interviews to
capture patients’ detailed perceptions. A thematic analysis was performed by 2
independent judges.

Results: Participants were mostly male (n=11; 61.1%), with a mean age of 58.4
(SD=8.3) years old and a mean FEV1 percentage predicted of 43.1 (SD=17.7%). Patients
were mainly concerned about the progression of their condition (n=10; 55.5%) associated with the deterioration of their physical capacities (n=5; 27.8%)
and becoming older (n=3; 16.7%). Fears about being on their own (n=3; 16.7%)
and dying due to their respiratory disease (n=9; 50%), particularly dying of
asphyxiation (n= 6; 33.3%), were also reported by patients.

Conclusions: The results suggest that patients with COPD have significant
Concerns and fears about the irreversible process of their disease. Adequate knowl-
edge about these aspects will allow health professionals to adjust pulmonary
rehabilitation programs considering the patients’ emotional needs.

151. Mechanisms of allergic inflammation of the airways

1398
LSC 2011 Abstract: Different biochemical properties of house dust mite
induce divergent epithelial and inflammatory responses
S. Post, M. C. Nawijn, A. J. M. van Oosterhout, Irene Heijink. Pathology &
Medicine, Department of Allergology & Pulmonary Diseases, University Medical
Center Groningen, Groningen, NE.

Introduction: Allergic asthma is mainly caused by exposure to allergens like
house dust mite (HDM), when transepithelial delivery is facilitated by disruption of
the epithelial barrier.

Objective: We aimed to gain more insight in which biochemical property of
HDM is critical for the disruption of barrier function and initiates an inflammatory
response.

Methods: HDM extracts with different biochemical properties were analyzed for their
effects on airway/bronchial epithelial barrier function by measuring changes in
transepithelial resistance and immunostaining of the functional proteins ZO-1,
claudin and E-cadherin. Furthermore, we examined the induction of a pro-
flammatory phenotype of human bronchial epithelium by these HDM extracts, as
well as the epithelial remodeling and airway inflammation in vivo in a mouse model.

Results: We found that the different HDM extracts induced divergent responses. Importantly, the extract with lowest serine protease activity induced the most pro-
nounced effects on barrier function in vitro, and induced an increased production
of IL-25 in vivo. Remarkably, the same HDM extract induced HDM-specific IgE, a profound epithelial E-cadherin deelocalization, goblet cell hyperplasia, cellular inflammation and increased levels of CCL17 and IL-5 in vivo.

Conclusion: Together, these results indicate that the disruption in epithelial bar-
rier function is independent of serine protease activity, and is essential for allergic
sensitization and airway remodeling in vivo.

1399
2011 Abstract: The influence of glucocorticoid therapy on transcription
factor balance in asthma patients
Roxana Bumbacea, Stephen Durham, Carsten Schmitz- Weber. Respiratory
Medicine - Allergy, NHIF - Royal Brompton Hospital, London, GB. Allergy, Elias
Hospital Bucharest, Bucharest, RO. Allergy and Molecular Biology, Zentrums für
Allergie & Umwelt (ZAUM), Munich, DE.

Background: Transcription factors are important in T-cell subset differentiation as
well as clonal expansion and determine the polarization process towards different
T cell phenotypes. Glucocorticoids are important for asthma treatment, potentially
by modulating T cell differentiation. We hypothesize that the transcription factor
balance could be of predictive value in the treatment of asthma. Our study aimed to
profile T-cell transcription factors after 8 week GC-treatment of steroid naive
asthmatic patients and to test the steroid sensitivity of Th2 versus Th1 and Treg
transcription factors (TF) after a treatment period, which is known to control
Th2-cell activity and improve clinical symptoms.

Methods: Human CD4+ T-cells were isolated from steroid naive atopic asthmatic
patients. In vitro and after successful inhalative GC-treatment, TF mRNA levels
were determined using real-time RT-PCR. Additionally, CD4+ T-cells from healthy
donors were exposed to a serial dilution of GC in the presence of Th1, Th2 or Treg
polarizing conditions and analyzed for gene expression after 48h.

Results: After 8 week GC-treatment, RORC2, T-Bet and GATA-3 did not show
significant changes, FOXP3 was slightly higher. In contrast the Th2-gene Gfi-
1 was significantly more highly expressed in asthma patients compared to healthy
individuals and decreased significantly following GC treatment. In vitro analysis
revealed that Gfi-1 is abundantly expressed in Th2-polarizing conditions in asthma
and displays dose-dependent sensitivity to GCs.

Conclusion: The current study shows for the first time that Gfi-1 is involved in
allergic asthma and may represent a biomarker for assessing Th2-dependent
disease and GC-responsiveness.

1400
PGD2 biosynthesis in several human mast cell models is catalyzed by
cyclooxygenase-1
Jeong-Hee Choi1,2, Sven-Erik Dahlén2, Gunnar Nilsson3. 1Clinical Immunology
and Allergy Unit, Department of Medicine, Karolinska Institutet, Stockholm,
Sweden; 2Experimental Asthma and Allergy Research Unit, The National Institute
of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Background: Mast cells and eicosanoid mediators play an important role in
asthma. There are few studies comparing eicosanoid release from different human
mast cell models.

Objective: We characterized release of eicosanoids from the LAD2 human mast
line cell and primary cultured-human mast cells from cord blood (CBMC) and
peripheral blood (PBMC).

Methods: Mast cells were stimulated with anti-human IgE via cross-linking of IgE
antibodies for 30 minutes, and β-hexosaminidase, cysteinyl leukotrienes (CysLTs),
LTB4, prostaglandin D2 (PGD2) were measured, and expression of cyclooxygenase
(COX)-1 and COX-2 were studied by western blot.

Results: LAD2 released β-hexosaminidase and PGD2 after stimulation with
anti-human IgE in a dose-dependent manner, but not CysLTs or LTB4, CBMC and
PBMC showed significant increase of CysLTs and LTB4 in addition to β-
hexosaminidase and PGD2, after stimulation. IL-4 priming did not enhance CysLTs
release in any of the mast cell models. IL-4 primed LAD2 however showed signifi-
cant enhancement of PGD2 release. The PGD2 release from the three human mast
cell models was consistently abolished by the selective COX-1 inhibitor, FR222347
(10(-5) M), but not by the COX-2 inhibitor, etoricoxib. There was strong COX-1
expression in LAD2 which showed significant inhibition of PGD2 release after
treatment with COX-1 siRNA.

Conclusion: LAD2 is a good model for studies of PGD2 release, but not for
CysLTs. The PGD2 release from the isolated human mast cells is dependent on
COX-1, in line with recent in vivo findings in asthmatics (Daham K et al. Clin
Exp Allergy 2011;41:36-45).

This abstract was supported by ERS/Marie Curie joint research fellowship (MC
1549-2010).

247s
1401

Alpha-melanocyte stimulating hormone potentially inhibits basophil activation, indicating a novel function of this neuropeptide in airway allergy
Ulrike Raap1, Manuelo Gehring2, Thomas Lugert2, Alexander Kapp1

Methods: Human basophils of patients with allergic rhinitis to grass pollen only

Results: Human peripheral blood basophils expressed MC-1Rs at protein and mRNA level. The MC-1R was functionally active in isolated basophils as shown by α-MSH-mediated intracellular increase of calcium 2+, α-MSH significantly inhibited anti-IgE, FMLP or PMA induced release of IL-4 and IL-6 (p<0.05). Further, α-MSH suppressed IgE or grass pollen induced basophil activation assessed with CD63 surface expression (p<0.01). The effect of α-MSH on basophil activation was MC-1R-mediated as shown by blockade with a peptide analogue of agouti signaling protein.

Conclusion: Our data show that α-MSH inhibits the allergic immune response in human basophils, presenting a novel and promising anti-inflammatory function of this peptide in allergic airway diseases.

1402

Local and systemic inflammatory responses following bronchial instillation of house dust mite allergen (HDM) and HDM/lipopolysaccharide (LPS) in mild asthmatics
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Rationale: Exposure to house dust, containing HDM and LPS, is associated with severity of allergic asthma. We hypothesized that adding LPS to bronchial provocation with HDM amplifies allergic inflammation in asthmatics on maintenance treatment with inhaled corticosteroids (ICS).

Aim: To assess the allergic inflammatory response in blood and bronchoalveolar lavage (BAL) fluid induced by provocation with HDM +/- LPS.

Methods: We included 39 mild asthmatic patients with HDM allergy. After 2 weeks run-in with fluticasone 100 μg bid, blood was drawn and subjects underwent bronchoscopy for instillation of saline in one lung followed by instillation of HDM +/- LPS in the contralateral lung. Six hours later, blood was drawn and BAL was performed. Statistical comparisons were made by Univariate Analysis.

Results: Additional instillation of LPS to HDM resulted in a significant increase in peripheral blood leukocytes and neutrophils, and a decrease of eosinophils. Provocation with HDM+LPS significantly increased total cell numbers, neutrophils, and Eosinophil Cationic Protein (ECP) in BAL fluid (p<0.04), and showed a trend towards an increase in eosinophils.

Conclusion: Additional instillation of LPS to a provocation with HDM in mild asthma decreases circulating eosinophils and increases pulmonary eosinophil influx and ECP-release, despite treatment with ICS.

1403

Poly(1-C)-induced responses in nasal and bronchial epithelial cells of patients with asthma and healthy controls
A.H. Wagener1, S. Luiten2, L.N. Venenkamp1, W.P. Kunsch1, P.J. Sterk1, C.M. van Drunen1, 1Dept. Pulmonology, Academic Medical Center, Amsterdam, Netherlands; 2Dept. ENT, Academic Medical Center, Amsterdam, Netherlands

Rationale: The majority of asthmatic exacerbations is associated with respiratory virus infection (Busse, Lancet 2010). Since airway epithelium is the primary site of a viral entry, we hypothesized that nasal and bronchial epithelia are equally responsive to respiratory viruses when measured as cytokine responses to poly(I:C).

Aim: We compared baseline cell activity and induced responses of primary human nasal and bronchial epithelial cells to poly(I:C) in allergic asthmatics and healthy controls.

Materials and method: This was a 2-group study in 8 allergic asthmatics (defined by GINA, PC20<8 mg/ml) with rhinitis (defined by ARIA) and 8 healthy volunteers. Both groups were instructed to take a controlled diet containing poly(I:C). Cytokine production was measured by Multiplex ELISA for 30 mediators and analysed by parametric analysis corrected for multiple testing.

Results: There were no significant between-group or within-group differences in baseline cell activity. Exposure to poly(I:C) induced up-regulation of several cytokines with no significant between-group differences. Asthmatics showed a higher activity for MIP-1β (p<0.009), MIP-1α (p<0.003), MCP-1 (p<0.038), and TNF-α (p<0.05) in nasal as compared to bronchial epithelial cells.

Conclusion: Expression is highly variable in individual subjects, and asthma- Nugenetic differences may explain these results. Further work is required to target peripheral lung inflammation in this patient group.

1404

Allergic mast cell expression of FcεRI differs between allergic asthma and rhinitis
Cecilia Andersson1, Ellen Tufvesson1, David Aronsson1, Anders Bergqvist1, Michiko Mori2, Leif Björner1, Jonas Erjefält2, Lund University, Respiratory Medicine & Allergology, Lund, Sweden; 2Lund University, Experimental Medical Science/Airway Inflammation, Lund, Sweden

Background: A significant proportion of patients with allergic rhinitis (AR) develop asthma. Our aim was to investigate expression of the high affinity IgE receptor (FcεRI) on alveolar mast cells in patients with AR with mild and uncontrolled asthma, AR with and without bronchial hyperreactivity (BHR) and non-atopic controls.

Methods: Bronchial and transbronchial biopsies from controls, patients with AR and patients with AR with concurrent asthma were processed for immunohistochemical identification of MC T and MC TC and their expression of FcεRI and bound IgE.

Results: The alveolar parenchyma in uncontrolled asthmatics had an increase in activities of both MCεRI (p<0.05) and MCεRI+ (p<0.003). In patients with AR with or without BHR and mild asthma no difference in tissue density of MCεRI or MCεRI+ was observed in central airways and alveolar parenchyma compared to controls. Mast cell expression of FcεRI was high in all groups in central airways. The expression of FcεRI on alveolar mast cells was increased in AR patients with concurrent mild (p<0.01) and uncontrolled (p<0.001) asthma compared to healthy controls. The asthmatics also had increased numbers of alveolar mast cells that expressed surface-bound IgE. A similar increase in mast cell FcεRI expression and surface-bound IgE was not seen in patients with AR with or without BHR.

Conclusions: Our data suggest that patients with atopic asthma have increased alveolar mast cell expression of FcεRI and surface-bound IgE compared to healthy controls and patients with AR with or without BHR. This might reflect a peripheral involvement of mast cells in the allergic asthma response and underscores the need to target peripheral lung inflammation in this patient group.

1405

Nlrp3/caspase-1-independent IL-1β production mediates diesel exhaust particles-induced pulmonary inflammation
Sharen Provoost1, Kurt Touwen1, Nele Pauwels1, Tom Vanden Berghe2, Peter Vandenabeele2, Bart Lambrecht3, Guy Foss1, Tania Maes 1, 1Department of Respiratory Medicine, Laboratory for Translational Research in Obstructive Pulmonary Diseases, Ghent University Hospital, Ghent, Belgium; 2Department for Molecular Biomedical Research, Unit for Molecular Signaling and Cell Death, Flanders Institute for Biotechnology, Ghent, Belgium; 3Department of Respiratory Medicine, Laboratory of Immunoregulation and Mucosal Immunology, Ghent University Hospital, Ghent, Belgium

Inhalation of diesel exhaust particles (DEP) induces an inflammatory reaction in the lung; however, the mechanisms are largely unclear. Interleukin (IL)-1β/IL-1RI signaling is crucial in several lung inflammatory responses. Typically, caspase-1 is activated in the Nlrp3 inflammasome, that recognizes several damage associated molecular patterns, which results in cleavage of pro-IL-1β into mature IL-1β. Here, we hypothesize that the Nlrp3/caspase-1/IL-1β pathway is critical in DEP-induced lung inflammation. Upon DEP exposure, IL-1RI KO mice showed reduced inflammation in the lung when compared to WT mice. In line, treatment with recombinant IL-1RI antagonist (anakinra) and IL-1β neutralization impaired the DEP-induced lung inflammatory response. Upon DEP exposure, Nlrp3 and caspase-1 KO mice, however, showed similar IL-1β levels and comparable inflammation in the lung compared to WT mice. In conclusion, these data demonstrate that the DEP-induced inflammation in the lung is mediated by IL-1β. This is in stark contrast with the inflammatory responses induced by LPS stimulation, where Nlrp3/caspase-1/IL-1β is critical.

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lungs acts through the IL-1/IL-1RI axis. In addition, DEP initiates inflammation independent of the “classical” Nramp3/caspase-1 pathway.

Funding: Fund for Scientific Research Flanders - Belgium (FWO Vlaanderen; Research Project G.052.06.e and G.0329.11N) and Interuniversity Attraction Poles (IUAP) - Belgian Science Policy P/035.

152. Dilemmas and progress in understanding childhood asthma

1406 Late-breaking abstract: MAGNETIC: a randomised, double blind, placebo controlled study of nebulised magnesium sulphate in acute asthma in children

Cecilia Powell, Department of Child Health, University of Cardiff, School of Medicine on behalf of the MAGNETIC Study Collaboration, Cardiff, Wales, United Kingdom

MAGNETIC is a double blind randomised placebo controlled study in acute asthma. Children between 2 and 16 years with acute severe asthma were randomised to receive standard care of three doses of nebulised salbutamol and intravenous ibuprofen every 20 minutes in the first hour with either placebo or nebulised magnesium (250mmol/L, 151mg/dose). Primary outcome was asthma severity score (ASS, 0-9) at 60 minutes post treatment; secondary outcomes were length of stay (LOS), need for intravenous (IV) bronchodilator therapy, need for PICU/intubation, stepping down of treatment at one hour, number of additional salbutamol administrations and serious adverse events.

506 children (median age 4.0 years; 58% male) were recruited from 30 centres. 251 children received treatment A and 255 children, treatment B. There were no clinical differences in baseline characteristics and no serious adverse serious events in either group.

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Difference between p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ASS T0 (SD)</td>
<td>4.72 (1.38)</td>
<td>4.95 (1.41)</td>
<td>-0.23 (0.05, 0.03)</td>
</tr>
<tr>
<td>Mean (SD) LOS (hours)</td>
<td>32 (25)</td>
<td>35 (27)</td>
<td>-2.94 (–7.52, 1.64)</td>
</tr>
<tr>
<td>Additional salbutamol doses (IQR)</td>
<td>8 (2-13)</td>
<td>8 (3-14)</td>
<td>0.00 (–1.1)</td>
</tr>
<tr>
<td>PICU/intubation (%)</td>
<td>18/243 (7)</td>
<td>7/252 (3)</td>
<td>0.05 (0.00, 0.10)</td>
</tr>
<tr>
<td>Need for IV treatment (%)</td>
<td>24/250 (10)</td>
<td>29/251 (12)</td>
<td>-0.02 (–0.08, 0.04)</td>
</tr>
<tr>
<td>Mean ASS T60 (SD)</td>
<td>4.72 (1.38)</td>
<td>4.95 (1.41)</td>
<td>-0.27 (–0.50, 0.03)</td>
</tr>
<tr>
<td>Mean LOS (hours)</td>
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<td>-0.02 (–0.08, 0.04)</td>
</tr>
</tbody>
</table>

There was no clinically significant difference in asthma severity score at 60 minutes post treatment. Treatment B significantly reduces the likelihood of intubation and need for intensive care admission.

1407 More airway smooth muscle in preschool children increases risk of future asthma

Ruth O’Reilly1, Tim Oates2, Jiayu Zhu3, Peter Jeffery3, Andrew Bush1, Sejal Saglani1.

1Respiratory Paediatrics, Royal Brompton Hospital, London, United Kingdom; 2Respiratory Medicine, Maastricht University Medical Centre, Maastricht, Netherlands; 3Surgery, University Medical Centre Utrecht, Utrecht, Netherlands.

### Introduction

Accurate prediction of future asthma in preschool wheezers is not possible. Reticular basement membrane (RBM) thickness and airway smooth muscle (ASM) are increased in school-aged asthmatic children [Reganey AJRCM 2008], but nothing is known about ASM changes in preschool wheezers, or the relationship of early airway pathology to future asthma.

### Aims

1) To measure RBM thickness and ASM in severe preschool wheezers and age-matched controls; 2) To relate preschool RBM thickness and ASM to school age asthma.

### Methods

Endobronchial biopsies (EBx) were obtained from preschool wheezers (n=47, median age 26 months) and non-wheezers (n=21, median age 15 months) undergoing clinically indicated bronchoscopy between 2002-2005 [Saglani AJRCM 2007]. 5μm sections were stained with haematoxylin & eosin. ASM was expressed as a proportion of the subepithelial area. ASM and RBM thickness were quantified using computer analysis. Children were followed up age 6-11 years to determine asthma status.

### Results

**Asthma:** At preschool age, ASM thickness was increased in wheezers (n=37, median 4.3μm) compared to controls (n=16, median 3.0μm), p=0.01. ASM was similar between preschool wheezers (n=28, median 0.08) and controls (n=14, median 0.077), p=0.97. 5168 (75%) children were followed up at school age.

- **School age:** Children with and without asthma had similar RBM thickness in their preschool EBx, p=0.23. However, children with asthma (n=8, median age 9.1 years) had increased preschool ASM (median 0.10) compared to those without asthma (n=24, median age 7.3 years, median ASM 0.066), p=0.007.

### Conclusion

Preschool children whose EBx had a higher proportion (>10%) of ASM had a 10-fold increased risk of asthma at school age.

1408 Remodelling of the bronchial mucosa in very young children with high risk for developing asthma

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Remodelling of the bronchial wall was thought to be a typical characteristic for asthma and the result of chronic inflammation. Structural changes were documented in bronchial mucosa of preschool children treated for asthma. We have very limited knowledge about the onset of immunological changes in very young children. The course of wheezing disorders in young age cannot be reliably predicted, so it is difficult to identify the most probable candidates for developing asthma.

The aim of our study is to identify abnormalities in the bronchial wall in children with high-risk of developing asthma. We examined endobronchial biopsies from 23 children under 4 years of age undergoing flexible bronchoscopy for clinical reasons others than recurrent wheezing. Twelve children fulfilled the criteria of Asthma Predictive Index, eleven children were in the control group. Thickness of the basement membrane was significantly higher in the high risk group than in the controls (on the average 4.14 μm vs. 3.5 μm respectively). On the other side, there seems to be no significant difference in the presence of neutrophil leucocytes and myofibroblasts between the two groups. This may correlate with the fact that all the patients were suffering from chronic or repeated respiratory problems for which they were indicated to bronchoscopy. However we suggest that first signs of remodelling like thickening of the basement membrane can be already present in children with high-risk of developing asthma in very early age. This may help us to improve therapeutic interventions in these children to prevent further development of irreversible morphological changes in later age.

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1409 Airway inflammation, lung function and wheezing phenotypes in preschool children

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### Background

Wheeze is a common symptom in preschool children. Currently, it is difficult to predict whether wheezing symptoms will pass or will persist and develop into asthma in later childhood.

### Aims

To prospectively study whether inflammatory markers in exhaled breath condensate (EBC) and pre- and post-bronchodilator interrupter resistance (Rint) assessed at preschool age, are able to predict wheezing phenotypes at five years of age.

### Methods

Children (N=227) from the ADEM study [1] were included. At preschool age (median (IQR): 3.3 (2.8-3.8) years), pre- and post-bronchodilator Rint was assessed. EBC was collected using a closed-glass condenser system. Inflammatory markers (Interleukin (IL)-2, IL-4, IL-8, IL-10, sICAM) were measured using multiplex immunoassay. Wheezing phenotypes were determined at five years of age via annual questionnaires.

### Results

Children were classified as: never- (n=47), early-transient- (n=89), intermittent- (n=46), and persistent wheezers (n=45) [2,3]. Children with persistent- and intermittent wheezes who had elevated levels of all interleukins compared with never wheezers (p<0.05). Moreover, children in the never- and transient wheeze group had slightly lower levels of baseline Rint compared with persistent wheezers (Median (IQR): 3.3 (1.1-7.7) vs. 1.4 (1.2-6.0) cmH2O/L, p<0.10).

### Conclusions

Children of the intermittent- and persistent wheeze group at age 5 years already had elevated inflammatory markers at preschool age, indicating augmented airway inflammation in these children.

### References

Airway inflammation is a continuous trait in children regardless of asthma symptoms

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Rationale: Elevated fractional exhaled nitric oxide (FeNO) and bronchial hyperresponsiveness are used as surrogate markers of asthma and children with persistent asthma.

Objective: To investigate the association between FeNO and bronchial responsiveness in a population of high risk children including the full spectrum from asymptomatic children to children with intermittent asthmatic symptoms and children with persistent asthma.

Methods: An unselcted group of 196 six-year-old children were included from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort born of mothers with asthma. Bronchial responsiveness was assessed as the relative change in specific airway resistance after cold dry air hyperperventilation. FeNO measurements were performed prior to the hyperperventilation test. The association between FeNO and bronchial responsiveness was assessed by generalized linear models.

Measurements and main results: Bronchial responsiveness and FeNO exhibited a significant and linear association. A doubling of FeNO corresponded to an 8.4% increase in airway resistance after challenge (95% CI: 3.7-13.1, p=0.006). There was no evidence of interaction with current asthma and stratified analyses showed similar associations in children with and without asthma.

Conclusions: FeNO and bronchial responsiveness are associated and continuous traits in the population regardless of asthma. This suggests bronchial inflammation may be present subclinically, and caution against the use of these surrogates marks for asthma should be maintained. Childhood asthma remains a clinical diagnosis and surrogate markers may only be used cautiously as supportive evidence.

Randomized placebo-controlled study of ciclesonide in preschool children with recurrent wheeze and a positive asthma predictive index or atopy

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Rationale: To assess the efficacy and safety of ciclesonide, versus placebo, in preschool children with recurrent wheeze and a positive asthma predictive index (API) or atopic sensitization.

Methods: Children 2-6 yrs with recurrent wheeze episodes were eligible if they had a positive API, or were sensitized to aeroallergens. Children with exclusive episodic viral wheezing were excluded. After a 2-4 week baseline period, patients with ongoing symptoms/rescue medication use were randomised to once-daily ciclesonide 40, 80, 160 μg or placebo for 24 weeks.

Results: The number of wheeze exacerbations requiring systemic steroids was unexpectedly low in all groups: 25 (10.2%) in placebo group, as compared to 11 (4.4%), 18 (7.3%), and 17 (6.7%) in ciclesonide 40, 80, and 160 μg, respectively.

Conclusions: In preschool children with recurrent wheeze and a positive API, ciclesonide is safe and effective in reducing exacerbations.

Opposite effect of endotoxin exposure with different MD-2 genotypes on asthma in children

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Background: Endotoxin exposure may play an important role in the development of asthma. MD-2 is a glycoprotein that assembles with TLR4 to form functional signalling receptor for endotoxin. We hypothesised that genetic variations in MD-2 may modify the relationship between endotoxin exposure and asthma.

Methods: Study population comprised 423 children with physician-diagnosed asthma and 414 non-asthmatic controls (age 6-18 years) recruited from the general hospital in Slavonski Brod, Croatia. We collected mattress dust sample and measured endotoxin content using kinetic limulus assay. We genotyped 9 haplotype-tagging SNPs in MD-2 (Sequence). Correction for multiple comparisons was carried out using Benjamin-Hochberg's False Discovery Rate (FDR) method.

Results: In the whole population, endotoxin exposure was associated with a decreased risk of asthma (aOR 0.75, 95%CI 0.58-0.98, p=0.03). None of the MD-2 SNPs was associated with asthma after FDR correction. For three SNPs, we identified a significant interaction between genotype and endotoxin exposure (G×E). The effect of endotoxin exposure on asthma may differ across children with different variants of the MD-2 gene.

Lessons learned from the epidemiology and natural history of asthma

Rationale: Patients with severe or difficult-to-treat asthma are an understudied population. The primary objective of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is to characterize the natural history of disease in the largest cohort of severe or difficult-to-treat asthma patients. We highlight the main findings of 25 research articles.

Methods: TENOR was a 3-year, multicenter, observational cohort study of 4,756 patients (n=3,489 adults ≥ 18 years; n=627 adolescents 12-17 years; n=637 children 6-11 years) Data was collected semi-annually and annually.

Results: Regardless of age, patients demonstrated high rates of HCU, despite receiving multiple long-term controller medications. Uncontrolled asthma, per the NHLBI guidelines, is highly prevalent and predictive of future asthma exacerbations in children and adolescents/adults. Children have an increased exacerbation risk and asthma burden compared with adolescents/adults. Increased weight is associated with worse asthma related outcomes. Aspirin sensitivity is associated with increased asthma severity and possible remodeling of both the upper and lower airways. Also, the phenotypes of persistent airflow are described. IGE and allergy play an important role in severe or difficult-to-treat asthma. Quantitative results not listed due to space constraints.

Conclusions: Patients with severe or difficult-to-treat asthma demonstrate an unmet need. The characterization of this cohort has improved our understanding of asthma control and exacerbations.

Flexible bronchoscopy in the diagnosis of paediatric lung diseases

Airway-related complications in preterm infants who were intubated at birth

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Background: Airway (AW) complications associated with intubation (IT) and mechanical ventilation (MV) have been observed in preterm infants (PTI). We describe their clinical manifestations (CM) and FB findings.

Methods: Fiberbronchoscopy (FB) was performed in symptomatic PTI who were intubated at birth. We describe their clinical manifestations (CM) and FB findings.

Results: AW complications in preterm infants who were intubated at birth (n=637 children 6-11 years). Data was collected semi-annually and annually.

Conclusions: Patients with severe or difficult-to-treat asthma demonstrate an unmet need. The characterization of this cohort has improved our understanding of asthma control and exacerbations.
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Brachoscopic and high resolution CT findings in children with chronic wet cough

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Background: Chronic wet cough strongly suggests endobronchial infection which, if left untreated, may progress to bronchiectasis. Our aim was to compare the efﬁcacy of bronchoscopy CT (HCCT) and high resolution bronchoscopy (FB) in detecting airway abnormalities in children with chronic wet cough and to explore the association between radiological and bronchoscopic/bronchoalveolar lavage (BAL) ﬁndings.

Methods: We retrospectively evaluated 93 children (0.6-16.4 years) with wet cough for more than 6 weeks referred to a specialized center and deemed unlikely to have asthma. All patients were submitted to hematological investigations, chest x-rays, HCCT, and FB/BAL. HCCT scores were correlated with the Bhalla method and bronchoscpic findings of bronchitis were grouped into 5 grades of severity.

Results: Positive HRCT were found in 70 (75.2%) patients, respectively (p=0.76). A positive correlation was found between Bhalla score and duration of cough (p=0.23, p=0.026). FB/BAL was superior to HRCT in detecting abnormalities (p<0.001). The Bhalla score correlated positively with the type IIR (OR: 5.44, 95%CI: 1.92-15.40, p=0.001) and type IV (OR: 8.91, 95%CI: 2.53-15.42, p=0.001) bronchoscopic lesions; it also correlated positively with the percentage of neutrophils in BAL (p=0.23, p=0.036).

Conclusions: HRCT detected airway wall thickening and bronchiectasis and the severity of the ﬁndings correlated positively with the length of clinical symptoms and the intensity of neutrophilic inﬁltration in the airways. However, HRCT was less sensitive than FB/BAL in detecting airway abnormalities. The two modalities should be considered complementary in the evaluation of prolonged wet cough.

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Foreign body aspiration in children: Single center experience during a 4 years period

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Introduction: Accidental Foreign Body Aspiration (FBA) is a cause of death in children. It requires early recognition and timely treatment to minimize the potentially dangerous side effects. The aim of our study was to determine the clinical spectrum, the demographic, and also the etiology of FBA in children.

Method: We retrospectively reviewed 188 pediatric patients with a history suggestive of foreign body aspiration over the 4 years from February 2007 to February 2011 in Children’s Medical Center affiliated to the Tehran University of Medical Sciences, Tehran, Iran.

Results: Foreign body was conﬁrmed in 112 children (59.5%) by rigid bronchoscopy. The mean age of the patients was 4 years, the 24 hours from the time of aspiration (early diagnosis). Fifty one of the patients had wheezing (24% unilateral, 27% bilateral), and 4% with no wheezing. Fifty ﬁve percent of foreign bodies were located in the right side, 35% in the left side, 8% in the trachea and 4.5% in the both sides. Of the 112 foreign bodies recovered, 87% were organic; 54% of these were sun ﬂower seeds. There was not any peanut among recovered foreign bodies in our series.

Conclusion: FBA should be excluded in children who have had a history of choking, persistent cough and chronic respiratory symptoms even in the presence of normal physical findings.

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BAL eosinophil counts and speciﬁc clinical phenotypes of atmatic and/or atopic children

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Eosinophils play an important role in the inﬂammatory process of asthma and allergy, but their role is still unclear. This study aimed to investigate whether BAL eosinophils could identify speciﬁc clinical phenotypes of asthmatic and/or atopic children. We analysed BAL and bronchial biopsies from 107 children undergoing ﬁberoptic bronchoscopy for appropriate indications: 26 astatic asthmatics (AAS), 28 non-atopic asthmatics (NAAS), 22 atotics without asthma (ANAS) and 31 non-atopic non-atotic controls (C). Total and differential cell counts, ECP and IL-8 were analysed in BAL. Inflammatory cells were also quantified in bronchial biopsies by immunohistochemistry. Based on BAL counts we grouped children into non-eosinophilic (BAL eos <1%), 90 children: 16 AAS, 24 NAAS, 20 ANAS. 30 C) and eosinophilic (BAL eos ≥2%; 17 children: 16 AAS, 24 NAAS, 20 ANAS, 30 C) and eosinophilic (BAL eos ≥2%; 17 children: 16 AAS, 24 NAAS, 20 ANAS, 1 C) age was similar in the two groups (median 5 yrs). Eosinophilic children showed more frequent increases in IgE, ECP, IL-8, BAL neutrophils and tissue eosinophils (p<0.01 for all). When the eosinophilic group was divided in intermediate (2% ≤ BAL eos <4%) and severe (BAL eos ≥4%), both groups had increased IgE, ECP and tissue eosinophils. Instead, IL-8 and neutrophil counts were increased in intermediate but not in the severe group (p<0.005). Severe eosinophilia was seen more frequently in children with difficult asthma (p=0.039).

In conclusion, BAL eosinophilia in our study was observed in 15.8% of children and severe eosinophilia in 7.5%. AAS were more frequent in the intermediate and severe eosinophilic groups; NAAS were equally distributed in the three groups and ANAS were present in the non-eosinophilic and severe eosinophilic group.
Bacterial cultures in bronchoalveolar lavage fluid in children with chronic respiratory conditions

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Background: The role of bacteria has usually been underestimated in children with chronic respiratory symptoms.

Aims: To describe the incidence of positive (+) bacterial cultures (BC) in bronchoalveolar lavage (BAL) fluid in children with chronic symptoms, and to assess differences between children with and without bronchectasis (BCE).

Methods: We carried out a review of all BAL performed from 2007 to 2010 in outpatients of our respiratory clinic. We defined 2 groups (gr: 1) BCE of unknown etiology, 2) Other chronic respiratory conditions with cystic fibrosis or receiving antibiotic treatment at the moment of the BAL were excluded. Chi2 test was used to assess differences between both gr and the association between gr 1 and the presence of purulent airway (AW) secretions. A multivariate logistic regression was built using gr as dependent variable; and gender, age, AW malacia and gastroesophageal reflex (GER) as independent ones.

Results: The final sample consisted of 70 children (56% male; gr 1: 23, gr 2: 47) who underwent a BAL at a median age 51.7±33.5 mo. BC was + in 48 (69%) children: 19 (83%) in gr 1 and 29 (62%) in gr 2 (p=0.077). Among + BC, the most common bacteria were H influenzae (n=28) and S pneumoniae (n=18), followed by S aureus (n=5), P aeruginosa (n=4) and K pneumo (n=2). A very significant association was found between gr 1 and purulent secretions (p<0.0001).

Conclusion: Although a + BC in BAL fluid is more common in children with BCE, the role of bacteria in other non-suppurative lung diseases should be taken into account.

1420 The role of transbronchial biopsy in pediatric patients

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Objective: To evaluate the use of transbronchial biopsies in pediatric lung diseases.

Methods: Retrospective review of transbronchial biopsies performed between 1998 and 2010. We analyzed the technique used, type of bronchoscope, complications, sample adequacy and diagnostic utility.

Results: We reviewed 137 biopsies, 25 were desimated for lack of information, so 112 biopsies from 47 patients were finally evaluated. Of these, 34 had received a lung or cardio-pulmonary transplant (age range, 6 months-22 years) and 13 were non-transplanted patients (18 months to 18 years). In 22 procedures, a 3.6 mm flexible bronchoscope was used (with forceps of 1.1 mm clips); in the rest we used a 4.9 mm bronchoscope (with 1.8 mm clips).

Conclusions: One hundred biopsies (90%) were adequate (91.2% of the biopsies performed with the 1.8 mm forcecs and 62.7% with the 1.1 mm forcecs). In the non-transplant population, biopsy was diagnostic in 75% (78% biopsied with the 1.8 mm, 11% with 1.1 mm forcecs; 11% unknown)

Cell acute rejection was diagnosed in 25% of the transplanted patients. Rejection was observed in 23% of all the biopsies and in 33% when we considered the symptomatic patients.

Complications included five pneumothorax (4.5%), three bronchospasms (2.7%) and nineteen bleeding (16.9%), 17 mild-moderate and 2 severe (1.8%), that stopped after instillation of cold saline and adrenaline

Conclusion: Transbronchial biopsy is a relatively safe and effective method for diagnosis and monitoring of lung diseases in selected children. We got a poor performance with the pediatric bronchoscope and forceps of 1.1 mm in our unit, so when possible the use of forceps 1.8mm might be preferable.
the mandibula measured just above the epiglottis correlated significantly with the change in upper airway resistance (R²=0.91, p<0.014). It could be concluded that stimulating the hypoglossal nerve changes the upper airway morphology. A relatively complex motion of the tongue base is observed with an enlargement of the airway lumen predominantly near the tongue base. Depending on the volume of the oral cavity, the enlargement is homogeneous or a decrease in cross-sectional area occurs at the palatal level. The distance between the tongue base and the mandibula appears to be a good surrogate for changes in upper airway resistance.

1424 Mechanical response to electrical- and neuro-stimulation of the genioglossus (GG) in propofol-sedated OSA patients
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Pharyngeal collapsibility during sleep is believed to increase primarily due to decline in dilator muscle activity. However, it is well documented that GG-EMG increases during apneas and hypopneas. The magnitude of increase is limited, however, as arousal terminates the respiratory disturbance. In the present study we prevented arousal by “drug-induced sleep” with propofol. We induced prolonged hypopneas in 17 patients with OSA by lowering CPAP after discontinuation of propofol, and monitored GG-EMG, flow and the area of (GAA) at the site of collapse (pharyngoscopy) until arousal. Prolonged hypopnea triggered a dramatic increase in GG-EMG. The mechanical response to this physiological drive to the GG was compared to baseline condition (after lowering CPAP from holding pressure), electrical stimulation (ES) of the GG, and after arousal.

Before arousal from sedation, flow remained unchanged despite the large increase in GG-EMG activity, while inspiratory CSA decreased. ES of GG, however, increased CSA and flow. Arousal resulted in fast enlargement of CSA and restoration of unobstructed flow, associated with marked reduction in GG-EMG. The mechanical response to this physiological drive to the GG was compared to baseline condition (after lowering CPAP from holding pressure), electrical stimulation (ES) of the GG, and after arousal.

<table>
<thead>
<tr>
<th>Drug-induced sleep</th>
<th>Awake</th>
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</thead>
<tbody>
<tr>
<td>baseline</td>
<td>GG-ES</td>
</tr>
<tr>
<td>CSA (mm²)</td>
<td>25.1±28.9</td>
</tr>
<tr>
<td>flow (l/min)</td>
<td>18.6±4.7</td>
</tr>
<tr>
<td>GG-EMG (max %)</td>
<td>4±6.3</td>
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</tbody>
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Methods: We assessed resting sympathetic outflow and sympathetic neurovascular transduction in newly diagnosed OSA without comorbidities (N=10) and in age-matched (N=10) and young (N=10) healthy controls. Sympathetic activity was directly measured (microneurography) at rest and in response to sustained isometric handgrip exercise. Neurovascular transduction was derived from the relationship of sympathetic activity and blood pressure to leg blood flow during exercise.

Results: Sympathetic activity in OSA was almost 2x the age-matched and 3x the younger controls. Neurovascular transduction was not different between OSA and age-matched controls, but was lower in younger controls. Among all subjects, resting activity was related to transduction (R² 0.12, p=0.04), however this relation was much stronger without those with OSA (R² 0.55, p<0.01).

Conclusions: Greater sympathetic activity in OSA does not appear to derive solely from lesser neurovascular transduction. Hence, other potential mechanisms associated with OSA per se likely result in greater sympathetic outflow. However, elevated outflow without lesser transduction may underlie the prevalent development of hypertension in this population.

1426 Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease
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Backgrounds and aims: Morbid obesity is frequently associated with low grade systemic inflammation, increased macrophage accumulation in adipose tissue (AT), obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD). It has been suggested that chronic intermittent hypoxia (CIH) resulting from OSA could be an independent factor for early stage of NAFLD in addition to other well-recognized factors (dyslipidemia, insulin resistance). Moreover, macrophage accumulation in AT is associated with local hypoxia in fat tissue. We hypothesized that the association between CIH and morbid obesity could exert additional specific deleterious effects both in liver and adipose tissues.

Methods: 101 morbidly obese subjects were prospectively recruited and underwent bariatric surgery during which a liver biopsy as well as subcutaneous and omental AT biopsies were obtained. Oxygen desaturation index (ODI) quantified the severity of nocturnal CIH.

Results: Liver biopsy analysis demonstrated that NAFLD lesions (ballooning of hepatocytes, lobular inflammation), NAFLD activity score (NAS) and fibrosis were more severe in patients with the highest ODI tertile (p values <0.001 for all hepatic lesions). In multivariate analysis, after adjustment for age, obesity and insulin resistance status, CIH remained independently associated with hepatic fibrosis, fibroinflammation and NAS. By contrast, no association was found between CIH, macrophage accumulation and adipocytes size in both subcutaneous and omental adipose tissue.

Conclusions: In morbidly obese patients, CIH was strongly associated with more severe liver injuries but did not worsen obesity induced macrophage accumulation in adipose tissue depots.

1427 The impact of obstructive sleep apnea syndrome on superoxide dismutase-1 activity in erythrocytes of high risk for type 2 diabetes (pre-diabetic) males Szczenz Nacosta1, 2, Edward Wysocka3, 2, Tomasz Piorunkiewicz1, Małgorzata Rywnikowska1, Lech Tolinski2, Halina Banara-Gabryel1, 1Department of Respiratory Medicine, Poznan University of Medical Sciences, Poznan, Poland; 2Department of Clinical Biochemistry and Laboratory Medicine, Poznan University of Medical Sciences, Poznan, Poland

Introduction: The relationships between obstructive sleep apnea syndrome (OSAS) and cardiovascular risk factors are under wide-world interest.

The aim of the study was to analyze superoxide dismutase-1 activity in erythrocytes of high risk for type 2 diabetes (pre-diabetic) males, due to a severity of OSAS diagnosis.

Methods: OSA suspected males with no acute or severe chronic disease were enrolled. Non-smoking Caucasians aged 30-63, with BMI 25-39.9 kg/m², submitted clinical, biochemical and polysomnographic examinations. EMBLA device was used to test severity of OSA episodes. The results of oral glucose tolerance test allowed to select pre-diabetic males. Apnea/hypopnea index (AHI) categorized patients for: OSAS (n=14, aged 53±7, AHI 0-4.9), OSAS1 (n=14, aged 55±8, AHI 5-15), OSAS2 (n=14, aged 56±5.5, AHI 16-30); OSAS3 (n=14, aged 55±7, AHI >31). Plasma glycerol, fasting lipid profile (TC, HDL-C, LDL-C, TG), uric acid were estimated. Fasting serum insulin (ELISA BioSource, Sunrise
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CPAP effects on leptin and visceral fat in patients with sleep apnea:
Double-blind, randomized, controlled trial
Peelin Lee1, Chih-Wei Yu2, Ming-Tzer Lin3, Tiffany Ting-Fang Shih4, Wen-Fei Shau2, Huey-Dong Wu5, Ching-Ting Tang1, Sandy Huey-Jen Hu6, Shieh-Chin Wang3, Chong-Jen Yu4, Pan-Chyr Yang3.
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Rationale: Obstructive sleep apnea (OSA) is common in obesity. Leptin plays an important role in controlling appetite, energy expenditure, and body fat deposition. Studies investigating the effect of continuous positive airway pressure (CPAP) on leptin have conflicting results. The major confounder is the visceral obesity. 

Objectives: We tested the stored blood from a double-blind, randomized, placebo-controlled trial aimed to (1) determine the CPAP effect on leptin and visceral fat and (2) investigate if changes of visceral fat after CPAP correlated with leptin in OSA patients.

Methods: Ninety-six patients were randomized to 12-week therapeutic (n=48) or subtherapeutic group (n=48). CPAP was measured the levels of leptin from stored blood and measured visceral fat with abdominal MRI. Results were analyzed with the intention to treat. The multiple linear regression was used to measure correlation between changes of visceral fat with changes of leptin.

Results: Eighty patients completed the study and 16 withdrew. 12-week therapeutic CPAP did not modify leptin and visceral fat compared to subtherapeutic group although significant improvement of objective sleepiness. The regression analysis identified that changes of visceral fat independently correlated with changes of leptin (coefficient 1.531, P=0.001, 95% CI (0.056 to 2.95)).

Conclusions: 12-week CPAP treatment does not modify leptin and visceral fat and changes in visceral fat independently correlate with changes of leptin. CPAP therapy should be combined with other measures that can reduce visceral fat when managing OSA patients.

1429 Predictors of recurrence in patients undergoing cryoballoon ablation for treatment of atrial fibrillation: the independent role of sleep disordered breathing
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Introduction: In patients with atrial fibrillation (AF) undergoing pulmonary vein isolation, cryoballoon technique (cryoPVI) has been adopted in many centers. This study aimed to evaluate predictors of AF recurrence including impact of sleep disordered breathing (SDB).

Methods: In 82 patients consecutively assigned to cryoPVI cardiorespiratory screening for SDB, assessment of medical history, ECG, echocardiography, standard laboratory measurement, and blood gas analysis were performed prior to intervention. After 3 months blanking period 7-days Holter ECG was performed at 3, 6 and then every 6 months to determine AF recurrence.

Results: 75 patients (69 paroxysmal AF; 6 persistent AF, 22 female, age 60±9 years) completed at least 6 month follow-up. Median follow-up of 12 months (interquartile range 6 to 18 months) confirmed maintenance of sinus rhythm in 69.4% of these patients. Stepwise forward regression model revealed moderate to severe SDB (cut-off apnea-hypopnea-index (AHI) ≥ 15; Hazard Ratio (HR) 2.95, p=0.04), early recurrence of atrial fibrillation (HR 8.74, p<0.001), persistent atrial fibrillation (HR 7.16, p<0.001), pre-procedural class III-antiarrhythmic drug treatment (HR 3.63, p=0.02), but not SDB per se (AHI ≥5b) as independent predictors for AF recurrence.

Conclusion: Moderate to severe SDB is a treatable condition that independently predicts AF recurrence in patients undergoing cryoPVI. Screening for SDB and adequate treatment may improve long-term success of cryoPVI.
distribution, provide lobar Raw and pressure. The difference in lobar pressure and
tegogether with lobar inflow, provide lobar S.
Results: Results show that the lobar S profile has a similar shape and as the flow
profile: The lobar S profile is constant during expiration. During inspiration lobar
S does increase exponentially near the end of the inspiration. Furthermore it can
be seen that both Raw and S do vary significantly between the different lobes.
Conclusions: Lobar Raw and S can be obtained through 2D updated with CFD by
taking a CT scan and a simultaneous flow and peso measurement. Information on
these lobar properties can be used to predict the outcome non-invasive ventilation.

1432
HOT HMV UK: An investigation into mechanisms of action of home mechanical ventilation (HMV) following acute hypercapnic exacerbations of COPD
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National Heart and Lung Institute, Respiratory Biomedical Research Unit, Royal Brompton Hospital and Imperial College, London, United Kingdom;
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Introduction: HMV in COPD remains controversial. Current data indicates improvements in arterial carbon dioxide (PaCO2) are mediated by improved pulmonary mechanics and hypercapnic ventilatory response (HCVR). This hypothesis has yet been to test in a controlled trial and no studies have investigated changes in neural respiratory drive (NRD) measured by parasternal EMG (EMG para).

Method: Patients with persistent hypercapnia (PaCO2 > 7 kPa) 2-4 weeks after resolution of an acute exacerbation of COPD were randomised to home oxygen therapy (HOT) or HOT and HMV. Baseline studies included HCVR and EMG para.

Results: 20 patients have been recruited and randomised. There was a significant between group difference in HCVR and NRD.

Follow up data is presented on 9 patients. Ventilator settings were IPAP 28±1, EPAP 5±1, RR 15±1. Significant improvement in both PaO2 and PaCO2 only occurred in the HMV group.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>HOT (n=10)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>FEV1</td>
</tr>
<tr>
<td>PaCO2</td>
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<td>PaO2</td>
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</table>

There was a significant between group difference in HCVR and NRD.

Follow up data is presented on 9 patients. Ventilator settings were IPAP 28±1, EPAP 5±1, RR 15±1. Significant improvement in both PaO2 and PaCO2 only occurred in the HMV group.

Conclusions: These preliminary data suggest that the addition of HMV to HOT in this group is associated with improvements in gas exchange and this appears in part mediated by changes in HCVR and NRD suggesting “resetting” of central drive.

1433
Polysomnography (PSG) under NIV in stable COPD to reduce patient-ventilator asynchrony (PVA) and morning breathlessness
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Introduction: Patient-ventilator asynchrony (PVA) is frequent in COPD patients considered yet effectively treated by NIV.

Objective: To assess whether adjusting ventilator settings during polysomnography (PSG) might improve patient-ventilator synchronization, sleep quality and morning dyspnea (“deviation dyspnea”).

Methods: 8 consecutive severe COPD patients (6±1.8 yrs, FEV1 30.4±8.7% of predicted values) were recruited and treated with NIV after PSG recording. PSG was performed in 20 patients receiving NIV and in a subgroup of 10 patients during NIV and HMV. HMV and NIV were performed in 10 patients in 20% of time of recording. Each night the patient received 60 minutes of NIV (active valve circuit (AVC) or leak circuit (LC) with and without additional artificial leak (4mm I.D.) next to the fullface mask). PaO2 was measured at the site of oxygen (FiO2-ventilator) as well as mask (FiO2-mask) following expiration system (AVC or LC) and opened or closed artificial leak. Capillary blood gas analyses were performed at start and end of each measurement.

Results: Overall, FiO2-mask (29±5%) was lower compared to FiO2-ventilator (34±4%) with a mean (95% CI) difference of 5.1 (4.2 to 5.9, p<0.0001)%. With LC FiO2-mask decreased by 3.2 (2.6 to 3.9, p<0.0001)% compared to AVC (Figure). PaO2 tended to be 6.3±1.0 to 13.7±1.0 mmHg lower after 60 minutes of NIV comparing LC and AVC, p=0.08. Implementing an artificial leak FiO2-mask decreased by 5.7 (5.1 to 6.4, p<0.0001)% (Figure) with lowered PaO2 of 10.4 (3.1 to 17.1, p<0.0001) mmHg.

Conclusions: Leak circuits regularly used for exhalation during NIV and uninhibited air leaks significantly reduce FiO2 in patients receiving NIV and O2, which substantially deteriorates patients’ oxygenation.

1435
Monitoring of non-invasive ventilation: Is the strategy used in daily practice enough?
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Background: Non-invasive ventilation (NIV) is recognized as an effective treat-
ment in respiratory failure. However, empirically determined NIV settings may not achieve optimal ventilatory support. As a result, NIV should be systematically monitored. Current strategy used for this monitoring includes clinical assessment, arterial blood gases (ABG) and oximetry. Ideally, complete polysomnography should be done but actually this practice is infrequent. Simple tools such as capnography (TcPCO₂) or built-in ventilator software (VPA/P-Reslink) provide useful information but their role should be defined.

**Objectives:** To determine effectiveness of current strategy versus different simplified tools in assessing NIV effectiveness.

**Methods:** Efficacy of NIV was assessed in 95 patients. They underwent oximetry, TcPCO₂, Reslink and ABG during spontaneous ventilation. Subjective comfort of NIV was evaluated by questionnaire. Results: While the usual approach including oximetry and ABG considered 42 patients as correctly ventilated, only 10 patients (11%) are effectively treated as questioned, ABG, oximetry, TcPCO₂ and Reslink were normal. Therefore, current strategy gave a wrong estimate of NIV quality in 34% of patients. Adding Reslink to this strategy recognized 20 patients as inadequately ventilated whereas adding TcPCO₂ allowed to identify 8 patients.

An alternative non-invasive strategy combining Reslink and TcPCO₂ identified 21 patients with good NIV performance. Among them, 8 (9%) had pathological ABG and were badly classified.

**Conclusion:** The usual strategy overestimates quality of NIV. Combining Reslink and TcPCO₂ allows detecting NIV failure in 75% of patients without ABG.

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1436

**Impact of three back-up rate (BUR) on subjective quality of sleep (QoS) and residual events in obesity-hyperventilation (OHS) patients with three simplified tools**

**Aim of study:** To compare the impact of spontaneous ventilation (SV; BUR=0), low BUR (10.9±0.9/min) and high BUR (20.5±1.5/min) applied in random order during 3 consecutive nights in OHS patients. Main outcome: Sleep structure assessed PSG Secondary outcome: Hyperventilation and residual events.

**Methods:** Infusion of non-invasive ventilation (NIV) was performed for sleep structure, obstructive (OE), central (CE) and mixed (ME) respiratory events, % time spent with patient ventilator asynchrony (PVA) and nocturnal hyperventilation measured by TcPCO₂. Two questionnaires assessed subjective QoS.

**Results:** Ten stable OHS patients under long term NIV (mean±SD; aged 55.7±9.2 yrs; BMI 48.5±5.4 kg/m², PaCO₂; 5.5±0.7 kPa) were included. Table 1 depicts main results.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Average SpO₂ (%)</strong></td>
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<tr>
<td>SV (57)</td>
</tr>
<tr>
<td>Low BUR (45)</td>
</tr>
<tr>
<td>High BUR (48)</td>
</tr>
<tr>
<td><strong>Diaphragm (59)</strong></td>
</tr>
<tr>
<td><strong>Micro Arteries (58)</strong></td>
</tr>
<tr>
<td><strong>Respiratory Events Index (64)</strong></td>
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<tr>
<td><strong>Central Arteries (61)</strong></td>
</tr>
<tr>
<td><strong>Mixed Arteries (58)</strong></td>
</tr>
<tr>
<td><strong>Diastolic Arteries (55)</strong></td>
</tr>
<tr>
<td><strong>Systolic Arteries (47)</strong></td>
</tr>
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</table>

ODL, CE, ME and time spent with PVA were all much higher with SV than with either low or high BUR. Subjective QoS did not differ between SV and low BUR. However subjects with high BUR perceived more awakenings and a lower QoS than with low BUR whereas their Sleep efficiency was lower.

**Conclusion:** In stable OHS patients under long term NIV, SV was associated with a very high rate of ODL, CE and ME when compared to low and high BUR. High BUR was perceived as less comfortable than low BUR.

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1437

**Diffusion weighted MR can improve preoperative lung cancer diagnosis**

**Johan Coolen 1, Frederik De Keyzer 2, Paul De Leyn 3, Johan Vansteenkiste 3, Walter De Wever 4, Herbert De Caluwe 2, Christophe Dooms 2, Eric Verbeken 4, Willy Coosemans 5, Dirk Vauzermont 6, Yolande Lievens 1.**

**Purpose:** Since diffusion-weighted MR (DW-MR) has shown promise in differentiating benign from malignant disease in several oncologic applications, we aimed to evaluate the potential role of this technique in differentiating benign from malignant lung lesions.

**Material and methods:** 50 patient staged with PET-CT and operated because of proven lung cancer or having a suspicious lung opacity were included. DW-MR was performed one day before surgery. PET-CT was evaluated first by visual inspection of all MR images by a chest radiologist and second by calculating the ADC values. Both PET/CT and DW-MR findings were correlated with pathology.

**Results:** Good correlation was found between DW-MR and pathology (κ=0.56, p<0.0001), whereas PET/CT performed worse (κ=0.20, p=0.1457). In total, 33 patients were diagnosed correctly with PET/CT, 7 incorrectly and 10 undetermined. DW-MR staged 45 patients correctly and 5 incorrectly. The 10 undetermined cases on PET/CT were correctly diagnosed on DW-MR. Pure ADC-average based diagnose showed an optimal threshold of 0.00152 mm²/s between benign and malignant lesions, with sensitivity and specificity of 91 and 57% respectively.

**Conclusion:** DW-MR could become an appropriate diagnostic instrument for preoperative lung cancer patients in the near future because it has a high accuracy for differentiating benign from malignant lung lesions.

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1438

**Comparison of four-dimensional (4D) CT ventilation imaging with SPECT/V/Q scans**

**Tokihiro Yamamoto 1, Sven Kabus 2, Jens von Berg 2, Cristian Lorenz 2, Michael Goris 1, Billy Loo 1, Paul Krafl 1.**

**Background:** A novel ventilation imaging method based on 4D-CT has advantages over existing methods. However, little validation has been performed.

**Purpose:** To compare 4D-CT ventilation imaging (VCT) with SPECT ventilation (VPECT) and perfusion (QPECT) scans.

**Methods:** VCT, VPECT and QPECT were acquired for 3 patients. VCT was compared with VPECT and QPECT. The spatial overlap of defects was assessed using the dice coefficient (DC). The defects were determined by (1) thresholding the SPECT images with 20%, 30% or 40% of the maximum value in the lung and (2) segmenting the same volume with lower values in VCT.

**Results:** VCT was of higher resolution than SPECT. Figure shows example images. Visually, regions of both agreement and disagreement were identified.
Table shows DCs (mean±SD) between the V_{QC} and V_{SPECT} or Q_{SPECT} defects. V_{SPECT} suffered from central airway depositions of aerosols, which drove extremely high correlations. There were moderate correlations with Q_{SPECT} in all patients. Lower thresholds yielded consistently lower DCs due to differences in low-value regions.

<table>
<thead>
<tr>
<th>Threshold</th>
<th>V_{QC} Defect</th>
<th>DC</th>
<th>Q_{SPECT} Defect</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>92±3.7</td>
<td>0.93±0.02</td>
<td>36±9.1</td>
<td>0.31±0.09</td>
</tr>
<tr>
<td>30%</td>
<td>98±1.0</td>
<td>0.96±0.01</td>
<td>61±3.8</td>
<td>0.69±0.09</td>
</tr>
<tr>
<td>40%</td>
<td>93±1.0</td>
<td>0.99±0.01</td>
<td>78±1.2</td>
<td>0.82±0.07</td>
</tr>
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</table>

Conclusions: The 4D-CT ventilation moderately correlated with the SPECT V/Q. Ongoing studies focus on investigating more patients and spatial characteristics of the differences.

1439 Micro-CT and 18F-FDG micro-PET of pulmonary fibrosis in mice induced by adenoviral gene transfer of TGF-β1

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Introduction: The morphological and functional information provided by micro-CT and micro-PET allows monitoring of acute and chronic disease states in small laboratory animals. We examined in-vivo micro-CT and micro-PET as non-invasive tools to assess pulmonary fibrosis in mice.

Material/Methods: Pulmonary fibrosis was induced in mice by intratracheal delivery of an adenoviral gene vector encoding biologically active TGF-β1. Respiratory gated and ungated micro-CT was performed in 18 mice at 1 to 4 weeks after pulmonary adenoviral gene delivery. In 5 additional mice 18F-FDG micro-PET and micro-CT was performed. Imaging was correlated to histopathology and findings in animals exposed to a control vector. Radiation doses were measured using thermoluminescence dosimeters.

Results: Significant correlation between Ashcroft histogram scoring and micro-CT was found for visual assessment scoring (p<0.001) and automated quantification by a region growing segmentation algorithm (p=0.004 for gated and p=0.006 for ungated exams). 18F-FDG micro-PET showed slight increase of glucose metabolism in the consolidated lung areas determined by micro-CT, which was coregistered to the micro-PET data using anatomical landmarks. Radiation doses for micro-CT ranged from 174 to 277 mSv. For micro-PET an expected dose of 140 mSv was calculated from the measurements.

Conclusion: Micro-CT and micro-PET allow valid visualisation of morphology and metabolism for the assessment of fibrosis in mice. The measured radiation doses allow serial examinations without deterministic radiation effects.

1440 Association of texture-based quantitative fibrotic patterns and pulmonary function test in a new validation set

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Background: Under non-volumetric CT scan, a texture-based quantitative lung fibrosis (QLF) score has been developed as a computer-aided diagnostic metric in a scleroderma-related interstitial lung disease (SSc-ILD) [1].

Objective: To test an association the QLF from CT score with pulmonary function tests in new study cohort.

Methods: From our anonymized research database, 119 subjects with SSc-ILD (mean age 48±10.6 years and 70.7% ±14.3 of FVC) underwent baseline CT scans with high-resolution, volumetric, 64 detectors in the prone position at full inspiration. The extents of fibrotic patterns were measured as a QLF score in 5 steps: 1) denoise images; 2) grid-sample at a fixed location; 3) convert the characteristics of intensities into texture features; 4) classify voxels as fibrotic or non-fibrotic patterns based on texture features and 5) report fibrotic voxels as percentages. Associations were tested by Spearman rank correlation.

Result: Correlations between pulmonary function test and QLF were similar in the previous study and this new cohort as shown below.

Conclusions: The quantitative fibrotic patterns in whole lung can be a useful prognostic metric of severity and the heterogeneity of distribution in fibrotic patterns in lobes can be used as an index.

Reference:

1441 Transthoracic echocardiography and pulmonary artery pressure assessment in patients with COPD exacerbation

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Background: Transthoracic echocardiography (TTE) is accepted as screening tool for pulmonary hypertension (PAP), whereas it is rarely performed in COPD patients due to possible difficulties caused by hyperinflated lungs.

Aims and objectives: The aim of our study was to find out whether it would be possible to predict if TTE is capable to assess pulmonary artery pressure (PAP) in patients with COPD exacerbation.

Methods: 40 consecutive patients with COPD exacerbation were enrolled. TTE directed for diagnosis of RV dysfunction, pulmonary function tests, blood gases, six minute walking test and BORG scale were performed at baseline and after successful treatment.

Results: It was possible to perform TTE in 17 (42.5%) subjects on admission and in 26 (65%) at discharge. PAP was present in 88.2% pre-treatment, and in 80.8% post-treatment (PAP mean±±25 mmHg), and in 35.3% pre-treatment and in 52.9% post-treatment (RVSP±±35 mmHg). It was possible to measure PAP using RVSP in 94.1% patients pre-treatment, and in 96.2% post-treatment, whereas it was possible to measure RVSP in 58.8% patients pre-treatment before, and 65.4% post-treatment. Simple as well as multivariable analysis did not find predictive value (p<0.05) of the following parameters: FEV1, FVC, IC, RV/TLC, TLC, ITGV, TLCO/VA, pO2, pCO2, 6MWT distance, BORG scale, GOLD (BMI), pack-years, spumon purulence to prognose possibility of obtaining accurate TTE results.

Conclusions: TTE may be used as an ineffective tool in assessment of PAPmean and in much smaller extent in assessment of RVSP in patients with COPD exacerbation, but it still seems impossible to predict in which patients it would be possible to perform accurate TTE.

1442 Mean eccentricity index strongly reflects mPAP in patients with IPAH using CINE cardiac MRI

Andrew Swift1,2, Smitha Rajaram2, Robin Condliffe1, Helen Marshall2, Dave Capener2, Judith Hurdman3, Charlie Elliot3, David Kiel3, Jim Wild2. 1Cardiovascular Biomedical Research Unit, National Institute of Health Research, Sheffield, United Kingdom; 2Academic Unit of Radiology, University of Sheffield, Sheffield, United Kingdom; 3Sheffield Pulmonary Vascular Disease Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Introduction: Left ventricular systolic eccentricity index (eEI) measured at echocardiography has been shown to correlate with pulmonary artery pressure (PAP) in patients with pulmonary hypertension (PH). This study assesses the relationship of eEI, diastolic eccentricity index (dEI) and mean eccentricity index (mEI) with mPAP in patients with idiopathic pulmonary arterial hypertension (IPAH) using CINE cardiac MRI.

Methods: We studied 36 patients with IPAH who underwent RHC and MRI within

Correlation between QLF and pulmonary function test

<table>
<thead>
<tr>
<th>p (p-value)</th>
<th>QLF score in the evaluation set [1]</th>
<th>QLF score in the new cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>-0.31 (p&lt;0.0001)</td>
<td>-0.53 (p&lt;0.0001)</td>
</tr>
<tr>
<td>DLCO</td>
<td>-0.35 (p&lt;0.0001)</td>
<td>-0.35 (p&lt;0.0001)</td>
</tr>
<tr>
<td>FEN1</td>
<td>-0.23 (p=0.0010)</td>
<td>-0.43 (p&lt;0.0001)</td>
</tr>
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</table>
157. Epithelial cells: role in health and disease

1443 Late-breaking abstract: Activation of the macrophage inflammasome by TLR3 ligation potentiates release of IL-8 and IP-10 from alveolar type II epithelial cell cultures from asthmatic but not normal donors

Davide Grandolfo, Andrew Thorley, Teresa Tetley. Lung Cell Biology, National Heart & Lung Institute, Imperial College London, London, United Kingdom

Recognition of microbial ligands by Toll-like receptors is central to the innate immune response of the peripheral lung to infection. This study investigated the effect of TLR3 ligation on cytokine release by primary human alveolar type II epithelial (ATII) cells and macrophages (AMs) alone and in co-culture. We hypothesised that TLR3 ligation elicits a distinct cytokine profile in both cell types which is enhanced by co-culture. Monocultures and co-cultures of ATII cells and AMs were exposed to the TLR3 ligand PolyIC for 24h. Both cell lines released IL-8 and IP-10 in response to PolyIC; co-culture significantly potentiated their release 4- and 5.7-fold respectively (P < 0.0001). The potentiation was not ATII-AM cell contact dependent; addition of Poly IC treated AM conditioned medium to ATII monolayers maintained the response whereas conditioned medium from ATII cells did not induce potentiated release from AMs. To elucidate which macrophage-derived cytokines were responsible for the potentiated response, neutralising antibodies were added to conditioned medium from AMs prior to incubation with ATII monolayers. Results demonstrated that neutralization of inflammasome-related cytokines, IL-1β and IL-18, significantly inhibited release of IL-8 and IP-10 (Table 1).

In conclusion, our study demonstrates that TLR3 ligands activate the AM inflammasome, inducing release of IL-1β and IL-18 which potentiates the innate immune response of the alveolar epithelium.

1444 Compressive forces stimulate release of TGFβ2 from differentiated bronchial epithelial cell cultures from asthmatic but not normal donors

Christopher Grange, Patrick Dennison, Donna Davies, Peter Howarth. Division of Infection, Inflammation and Immunity, Southampton University School of Medicine, Southampton, Hampshire, United Kingdom

Bronchoconstriction induces mechanical stress in the airways and normal bronchial epithelial cells respond by inducing profibrogenic responses. No studies have examined whether these responses are similar in asthmatic and non asthmatic populations. We tested the hypothesis that primary bronchial epithelial cells from asthmatic and non asthmatic donors respond similarly to mechanical stress mimicking bronchoconstriction by release of TGFβ2.

**Methods:** Bronchial epithelial cells (from healthy (n=9) and asthmatic (n=9) volunteers were obtained at bronchoscopy, expanded and grown at an air liquid interface (ALI). These were apically compressed with 5% CO₂ in air (30cm water pressure) for 1 hour, or sham compressed. 24 hours later total TGFβ2 was measured by ELISA in the basolateral medium.

**Results:** After sham compression, TGFβ2 release was similar in ALI cultures from healthy (median (IQR) 203.4 (143.8-271.7) pg/ml) or asthmatic (245.5 (162.3-276.6)) donors (p=0.67). After active compression, TGFβ2 significantly increased in the asthmatic ALI culture medium (median (IQR) of 299.4 (205.4-365.0)) (p=0.68). This change amounted to a median (IQR) difference of 29.7 (14.8-57.0) pg/ml in the asthmatic group and 11.6 (-35.6-48.7) in the healthy group (p=0.04).

**Conclusions:** Bronchial epithelial cells from asthmatic patients respond differently from normal cells to compressive force in vitro that mimics bronchoconstriction. This new finding suggests that there are at least two abnormalities in the asthmatic airway: the initial bronchoconstriction, and the epithelial response to it.

1445 SIRT6-induced activation of autophagy inhibits CSE-induced bronchial epithelial cell senescence

Naki Takaoka1, Jun Araya1, Hironori Hara1, Satoke Fujii1, Yoko Yumino1, Takatori Munata1, Makoto Kawashir1, Jun Hiroma1, Makoto Ootaka2, Toshikazu Morikawa3, Katsumi Nakayama1, Kazuyoshi Kuwano1. 1Division of Respiratory Diseases, Department of Internal Medicine, Jikei University School of Medicine, Minato, Tokyo, Japan; 2Division of Chest Diseases, Department of Surgery, Jikei University School of Medicine, Minato, Tokyo, Japan

**Introduction:** Senescence has been implicated in the pathogenesis of COPD, and tobacco smoke is known to induce cellular senescence. SIRT6, a class III histone deacetylase (HDAC), has been demonstrated to potentially antagonize cellular senescence. Autophagy, a lysosomal degradation pathway, is associated with cellular senescence.

**Aim:** To elucidate the regulatory role for SIRT6 in autophagy activation in terms of tobacco smoke-induced cellular senescence.

**Methods:** Primary HBEFC were used for the experiments. Senescence associated beta-galactosidase (SA-b-gal) staining and western blotting of p21 were performed to evaluate cellular senescence. SIRT6 expression vector and siRNA were transfected into HBEFC. To characterize autophagy, fluorescence microscopic detection of LC3-EGFP dot formation and western blotting for LC3, p62 were performed. Results: CSE-induced cellular senescence was inhibited by SIRT6 overexpression, while SIRT6 knock down increased the percentage of SA-b-gal positive cells. SIRT6 overexpression increased autophagy activation as shown by formation of LC3-EGFP dot and increased conversion from LC3-I to –II at basal level after CSE treatment. In contrast, SIRT6 knock down repressed autophagy activation. Furthermore, SIRT6-induced autophagy potentiated the accumulation of p62 expression after CSE treatment. SIRT6-induced autophagy regulated CSE-induced cellular senescence, because autophagy inhibition by knock down of LC3 diminished anti-senescence effect of SIRT6 overexpression.

**Conclusion:** These findings suggest the pivotal regulatory role of SIRT6 in autophagy activation and CSE-induced cellular senescence. SIRT6 might be a target molecule for the treatment of COPD.

1446 A three miRNA signature regulates the CF transmembrane conductance regulator (CFTR) in cystic fibrosis airway epithelium

Irene Oglesby1, Shane ONeill1, Noel McElvaney1, Catherine Greene2. 1Respiratory Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland; 2Respiratory Medicine, Beaumont Hospital, Dublin, Ireland

Expression profiling studies have identified altered miRNA patterns in several human diseases, however little is known of the role miRNA play in cystic fibrosis (CF). Here we examined the impact of altered miRNA expression in CF bronchial epithelium on CFTR expression.

We performed miRNA expression profiling on bronchial brushings taken from five CF and five non-CF individuals by qRT-PCR using Taqman Low Density Arrays (TLDA). Expression of altered miRNA was validated by qRT-PCR in additional brushings and in vitro in CF and non-CF bronchial epithelial cell lines. CFTR gene expression was also measured. miRNA inhibition and over-expression studies were performed in CFBE41o- and 16HBE14o- cell lines respectively in vitro and CFTR mRNA and protein was detected by qRT-PCR and western blot.

Of the 667 miRNA examined 56 were down-regulated and 36 up-regulated in CF. Here we examined the impact of altered miRNA expression in CF bronchial epithelium on CFTR expression.

1447 IL-17A induces glucocorticoid insensitivity in airway epithelial cells

Jan Zijlstra1, Nick ten Hacken2, Roland Hoffmann1, Antoon van Oosterhout1, Irene Heijink1. 1Pathology and Medical Biology, University Medical Center Groningen, Groningen, Groningen, Netherlands; 2Pulmonology, University Medical Center Groningen, Groningen, Netherlands

Glucocorticoids (GC) are the cornerstone of asthma treatment. However, a subset of asthmatic patients is insensitive, which is a problem in the management of asthma. Previous studies suggest that GC-insensitivity is associated with Th17 cells. Th17
cells act by producing inflammatory cytokines, including IL-17A. We aimed to assess whether IL-17A reduces GC sensitivity in airway epithelial cells and to elucidate the underlying mechanism.

We investigated the effect of IL-17A on the suppressive effect of budesonide (BUD) (10^{-5}-10^{-10} M) on TNF-α-induced IL-8 secretion and on Histone Deacetylase (HDAC) activity in the human bronchial epithelial cell line 16HBE with/without specific inhibitors for the ERK, p38 and PI3K pathways and upon overexpression of HDAC2.

We observed that IL-17A-induced IL-8 secretion is normally sensitive to GC in 16HBE, in contrast pre-treatment with IL-17A (2h) significantly reduces the sensitivity of TNF-α-induced IL-8 secretion to BUD. Immunodetection revealed that IL-17A activates the p38, ERK and PI3K pathways, but only inhibition of PI3K signaling reversed this GC-insensitivity. Our data suggest that IL-17A-induced GC-sensitivity is mediated by a reduction in HDAC2 activity, as IL-17A reduced HDAC activity, while overexpression of HDAC2 reversed IL-17A-induced GC-insensitivity. In contrast, IL-17A did not affect BUD-induced transcriptional activity, suggesting that IL-17A does not impair translocation of the ligated GC-receptor.

In conclusion, we show that IL-17A increases GC-insensitivity in bronchial epithelium which likely involves PI3K-dependent reduction in HDAC2 activity. IL-17A-induced GC-sensitivity may thus serve as a new target for therapeutic intervention in GC-insensitive asthma.

### 1448 Corticosteroid-dependent transcription is reduced by inflammatory stimuli in human airway epithelial cells: Rescue by long-acting β₂-adrenoceptor agonists

**Author:** Christopher Rider, Elizabeth King, Neil Holden, Mark Giemmbycz, Robert Newton. *Airways Inflammation Research Group, University of Calgary, Robert Newton; 2Childrens Hospitals and Clinics of Minnesota, Minneapolis, United States of America; 3Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, United States of America; 4Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 5Framingham Heart Study, Framingham, MA, United States of America; 6Department of Epidemiology and Biostatistics, University of Toronto, Toronto, Ontario, Canada; 7Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

**Rationale:** Inhaled corticosteroids (glucocorticoids) are the most effective treatment for inflammatory diseases such as asthma. However, in some patients with severe disease, or who smoke, or suffer from COPD, these drugs are less effective. While many investigators focus on the repression of inflammatory gene expression, corticosteroids also induce the expression (transactivation) of numerous genes to elicit anti-inflammatory effects.

**Results:** Using human bronchial airway epithelial, BEAS-2B, and pulmonary, A549, cells, we show that tumour necrosis factor (TNF) α, interleukin (IL)-1β, fetal calf serum (FCS), phorbol ester, cigarette smoke extract and a Gαδ-linked G-protein coupled receptor agonist, all attenuate simple glucocorticoid response element (GRE)-dependent transcription. With TNFα and FCS, this was not overcome by increasing concentrations of dexamethasone, budesonide or fluticasone propionate. Thus, maximal GRE-dependent transcription was reduced and this was confirmed for the glucocorticoid-induced gene, p57KIP2. Long-acting β₂-adrenoceptor agonists (LABAs), formoterol fumarate and salmeterol xinafoate, enhanced simple GRE-dependent transcription to a level that could not be achieved by glucocorticoid alone. In the presence of TNFα or FCS, which repressed corticosteroid responsiveness, LABAs restored corticosteroid-dependent transcription to that achieved by corticosteroids alone.

**Conclusions:** The transactivation of transactivation represents a mechanism to explain corticosteroid resistance and its reversal may explain the clinical benefit of LABAs as an add-on therapy in asthma and COPD.

**Funded by AstraZeneca.**

### 1449 Azithromycin fails to restore apoptosis in cystic fibrosis airway epithelium

**Author:** Erika Sutanto, Simone Caleo, Erika Sutanto2,3, Clara Foo1,2, Anthony Kicic1,2,3, Stephen Stick1,2,3, Erika Sutanto2,3, Clara Caleo1,2, Anthony Kicic1,2,3, Stephen Stick1,2,3, Wim Janssens1. *Funded by AstraZeneca.*

**Rationale:** Airway epithelium is primary target for respiratory viruses, especially human rhinovirus (HRV). Apoptosis as early host defense mechanisms is induced in response to viral infection. We have previously observed damped apoptotic & increased viral replication in cystic fibrosis (CF) airway epithelium compared to healthy controls. Azithromycin induces innate immune responses in non-CF epithelium. We hypothesize that addition of azithromycin to HRV-infected CF epithelium which likely involves PI3K-dependent reduction in HDAC2 activity.

**Conclusions:** The repression of transactivation represents a mechanism to explain corticosteroid resistance and its reversal may explain the clinical benefit of LABAs as an add-on therapy in asthma and COPD.

**Funded by AstraZeneca.**

### 158. Exercise training: new populations, new techniques

**1451 Preliminary results of pulmonary rehabilitation in interstitial lung diseases: A randomised controlled trial B32220095560**

Silvia Pérez Bogerd1, Wim Wuyts1, Veronica Barbier1, Daniel Lange1,2,3, Chris Burin1,2, Hans Van Remoortel1,2,3, Marc Decramer1, Thierry Troosters1,2,3, Wim Janssens1. *1Pulmonary Rehabilitation and Respiratory Division, UZ Gent/Ghent University, Ghent, Belgium; 2Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium.*

**Background:** Pulmonary rehabilitation (PR) is an excellent therapeutic option in chronic lung diseases, however there are little data on PR in interstitial lung diseases (ILD).

**Aims:** To report preliminary 3month outcomes of a randomised controlled trial evaluating the effects of PR on exercise capacity (Six Minute Walking Distance, 6MWD; Peak Work Rate, Wmax), quality of life (SGRQ, CRDQ) and muscle force (QF) in 50 ILD patients over 1year.

**Method:** Patients were randomly assigned to receive a PR program or usual medical care. Mean changes in outcomes were compared between the study arms.

**Results:** 3month data are currently available in 34 patients (table 1). 6MWD and Wmax increased significantly in the PR group compared to the control group (mean differences 67m [95%CI 34 to 101m] (figure 1) and 16W [95%CI 5 to 26W]). An improvement in QOL was also observed (SGRQ -12.5 [95%CI 18 to -7] and CRDQ 17.5 [95%CI 12 to 23]). Improvements in QF between both groups did not reach statistical significance (p=0.06).

**Table 1. Baseline characteristics of patients. Data as mean ± SD**

<table>
<thead>
<tr>
<th>Controls (n=17)</th>
<th>PR (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65±9</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>7/10</td>
</tr>
<tr>
<td>DLCO (%pred)</td>
<td>41±11</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>78±12</td>
</tr>
<tr>
<td>Wmax (%)</td>
<td>72±7</td>
</tr>
<tr>
<td>QF (W)</td>
<td>77±37</td>
</tr>
<tr>
<td>SGRQ (points)</td>
<td>38±17</td>
</tr>
<tr>
<td>CRDQ (points)</td>
<td>86±23</td>
</tr>
</tbody>
</table>

**Conclusion:** Although CF are more susceptible to HRV1b infection, the damped apoptotic response seen in CF epithelium after HRV infection cannot be restored with pre or co-treatment with azithromycin. The increased production of IL-8 observed post viral infection was not ameliorated following macrolide treatment.

**Funding:** NHMRC, ARC, ACFRT.
in conventional training, which shows that this device can be used with a more accessible option for resistance training in COPD.

1454 Non-linear exercise training is the preferred training method in patients with severe COPD
Peter Klijn1, Henk van Steeg2, Ton van Keimpema1,3, Rik Gosselink4, 1Department of Pulmonology, Asthma Center Heidehuij, Hilversum, Netherlands; 2Jüts Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Netherlands; 3Department of Pulmonology, Academic Medical Center, Amsterdam, Netherlands; 4Respiratory Rehabilitation, Katholieke Universiteit Leuven, Leuven, Belgium

Methods: COPD patients underwent exercise training 3-times/ wk for 12 weeks and were randomized to either NLE [N=36; FEV1, 31±9.2% pred, 61±7.1 yr, fat-free mass (FFM) index 15.4±2.6 (kg FFM/m²)] or combined endurance and progressive resistance training (Spruit et al EJR 2002) [EPR N=36; FEV1, 33±9.5% pred, 61±4.5 yr, FFM-index 15.2±2.3 (kg FFM/m²)]. NLE: resistance training with varying repetition zones based on maximum load (1RM): strength 1-3, 4-6, 8-10 reps, 50-85% 1RM; local muscle endurance 12-15, >20 reps, 30-50% 1RM; ergometer training with varying intensity zones (%maximum workload (Wmax) from maximum exercise test: 65%, 85%, 90%, 85%, 80%).

Results: After 12 weeks cycle endurance time at 75%Wmax increased in both groups with significant larger improvements with NLE training (387±158 to 1049±244sec) compared to EPR (384±268 to 631±364sec) p<0.001. The NLE group showed significant larger improvements compared to EPR for dyspnea 1,6±1.3 vs 0,1±0.1 and fatigue 1,4±1 vs 0.6±1.2 domains of Chronic Respiratory Questionnaire (p<0.01). Both groups showed similar improvements for emotional functioning 0.3±0.9 vs 0.8±1.1 and mastery 0.1±0.2 vs 0.1±1.2.

Conclusion: NLE is the preferred method of exercise training in patients with severe COPD compared to the present guideline based method because of better improvement of both endurance and health-related quality of life.

1455 Effects of whole body vibration in patients with COPD: A randomized study
Biyathy Sat, Eric Derron. Department of Respiratory Medicine, University Hospital Ghent, Ghent, Belgium

Introduction: Besides conventional resistance training (CRT), whole body vibration (WBV) has been shown to be effective. Effects of WBV in COPD patients have not been assessed so far.

Aim: To compare, the effects of WBV with those obtained by CRT on exercise capacity, muscle force and QoL.

Methods: Patients with COPD, referred for pulmonary rehabilitation, were randomized in one of two training groups. Patients in CRT group performed resistance training on multigym equipment and patients in WBV group trained on a FITVIBE.

Results: 70 patients with COPD, showed at baseline an impaired exercise capacity, muscle force and QoL, no significant differences were seen between groups. Both groups improved the exercise capacity, muscle force and QoL over time. There were no significant differences after training.

1456 Home-based rehabilitation program for lung cancer patients
Valentine Coats, François Maillais, Sébastien Simard, Éric Frechette, Didier Sacy. Pneumologie, Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada

Patients with lung cancer often experience a reduction in exercise tolerance and muscle weakness. Despite the well-recognized effectiveness of pulmonary rehabilitation, few researches have studied its impact in lung cancer patients, particularly among those awaiting for a lung resection surgery (LRS).

Objectives: To investigate the feasibility of a short home-based rehabilitation program (HHRP) in patients with lung cancer awaiting for a LRS and to determine its effectiveness on exercise tolerance and skeletal muscle strength.

Methods: Ten patients with lung cancer awaiting for a LRS were invited to a
159. Biomarkers and outcomes of community-acquired pneumonia

PI459 Does the serum C-reactive protein (CRP) predict adverse outcomes in patients admitted with community acquired pneumonia?
Gareth Walters, Hon Sum Liu, Monika Gemza, Farrukh Rauf. Respiratory Medicine, Worcestershire Royal Hospital, Worcester, United Kingdom

BTS guidelines on management of community acquired pneumonia suggest that failure of C-reactive protein (CRP) to resolve by ≥50% during admission predicts complication. We aimed to see whether a high CRP ≥50% at ≥24 days increases probability of effusion and death but is not a reliable marker of empyema or ITU admission.

In order to determine if some marker that can help us to predict complications in patients admitted with community-acquired pneumonia (CAP), we prospectively included 228 patients and studied leukocyte count (WBC), C-reactive protein (CRP), procalcitonin (PCT) and midregional proadrenomedullin (MR-proADM) in the first 24 hours of their admission. One hundred and forty six (64%) patients suffered 310 significant complications including 22 patients and studied leukocyte count (WBC), C-reactive protein (CRP), procalcitonin (PCT) and midregional proadrenomedullin (MR-proADM) in the first 24 hours of their admission.

In ROC analysis the best AUCs were PSI 0.729 and MR-proADM 0.706. The optimal cut-off to predict complications for MR-proADM was 0.833 mmol/L (sensitivity 67.3%, specificity 66.2%, positive likelihood ratio (LRH) 1.99 and negative likelihood ratio (LHR) 0.49. Findings for PSI class 4 and 5 were sensitivity 72.3%, specificity 62.3%, LRH 1.92 and LHR -0.44. Similar results were obtained when we compared patients with and without only respiratory complications. PCT and CRP, and especially MR-proADM and PSI score, appear to be useful in early identification of patients at risk for complications during hospitalization.
We studied the accuracy of white blood count (WBC) and 3 biological markers, C-Reactive Protein (CRP), Procalcitonin (PCT) and Proadrenomedulin (Pro-ADM) obtained in the admittance at Emergency Department, in predicting mortality of 224 patients hospitalized with Community Acquired Pneumonia (CAP).

ROC analysis showed that AUC for MR-proADM was significantly higher compared to those of PCT, CRP and WBC, and without significant differences when compared with PSI and CURB65.

Optimal cut-off to predict 30-day mortality for MR-proADM was 1.066 nmol/L. For 90 and 180-days mortality the optimal cut-off for MR-proADM was the same, 1.001 nmol/L, and for 1-year mortality, 0.998 nmol/L.

A logistic regression model combining MR-proADM levels with PSI score showed for 30-day mortality an optimal cut-off of 1.001 nmol/L, and for 1-year mortality, 0.998 nmol/L.

For 90 and 180-days mortality the optimal cut-off for MR-proADM was the same, 1.066 nmol/L, and for 1-year mortality, 0.998 nmol/L.

A threshold of PCT ≥ 0.5 rules out viral etiology with a very high negative predictive value. Legionella is associated with initial higher CRP. CPR and PCT do not allow to differentiate between viral or atypical etiology.

Background: Accurate severity assessment is important to guide initial management of patients with community-acquired pneumonia (CAP). Recognised severity scores may fail to recognise some high risk patients. Lactate is a powerful marker of sepsis but has not been studied in patients with CAP.

Methods: In a prospective study, arterial lactate was measured on admission in 855 patients with CAP. Recognised severity scores were calculated from admission data. The outcomes of interest were 30-day mortality and the need for mechanical ventilation or vasopressor support (MV/VS). The area under the receiver operator characteristic curve (AUC) and multivariable analysis adjusting for pneumonia severity were used to evaluate predictive markers.

Results: 30-day mortality increased with increasing arterial lactate level from 2.8% for lactate ≤2mmol/l, 17.9% for 2.1mmol/l-3.9mmol/l up to 30.8% in patients with lactate ≥4mmol/l (p<0.0001). Requirement for mechanical ventilation or vasopressor support increased with increasing lactate levels from 4.2% for lactate ≤2mmol/l, 15.6% for 2.1mmol/l-3.9mmol/l up to 36.4% in patients with lactate ≥4mmol/l (p<0.0001). Lactate had an AUC of 0.73 (0.70-0.77) for 30-day mortality, which was lower than that for CURB65-AUC 0.77 (0.74-0.80) and PSI-0.81 (0.78-0.84). Lactate had an AUC of 0.73 (0.70-0.77) for MV/VS which was equivalent to CURB65 and PSI.

Conclusion: A threshold of PCT ≥ 0.5 rules out viral etiology with a very high negative predictive value. Legionella is associated with initial higher CRP. CPR and PCT do not allow to differentiate between viral or atypical etiology.

P1463
Lactate is an independent marker of severity in hospitalised patients with community-acquired pneumonia
James D. Chalmers1, Aran Singanayagam2, Ahsan Akram2, Pallavi Mandal2, Gourab Choudhury3, Mavee Smuth1, Adam T. Hill2.
1MRC Centre for Inflammation Research, Queens Medical Research Institute, Edinburgh, United Kingdom; 2Department of Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Background: Accurate severity assessment is important to guide initial management of patients with community-acquired pneumonia (CAP). Recognised severity scores may fail to recognise some high risk patients. Lactate is a powerful marker of sepsis but has not been studied in patients with CAP.

Methods: In a prospective study, arterial lactate was measured on admission in 855 patients with CAP. Recognised severity scores were calculated from admission data. The outcomes of interest were 30-day mortality and the need for mechanical ventilation or vasopressor support (MV/VS). The area under the receiver operator characteristic curve (AUC) and multivariable analysis adjusting for pneumonia severity were used to evaluate predictive markers.

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Conclusion: A threshold of PCT ≥ 0.5 rules out viral etiology with a very high negative predictive value. Legionella is associated with initial higher CRP. CPR and PCT do not allow to differentiate between viral or atypical etiology.

P1464
An unbalanced inflammatory response on admission impacts clinical stability in hospitalized patients with community-acquired pneumonia (CAP)
Stefano Alberti1, Letizia Corrarna Mortachi1, Andrea Gramagina2, Barbara Dallari2, Samantha Galbiati2, Robert Cossarini2, Anna Maria Brambilla3, Fabio Giuliani3, Alberto Pesci4, Jose Bordoni4, Francesco Blasi5, 1Dipartimento di Medicina Clinica e Prevenzione, Università degli Studi di Milano-Bicocca, A.O. San Gerardo, Monza, Italy; 2Dipartimento Toracico-Polmonare e Cardio-Circolatorio, Università degli Studi di Milano, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; 3Dipartimento di Medicina d’Urgenza, IRCCS Fondazione Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy; 4Istituto di Medicina Intensiva, IRCCS Policlinico San Paolo, Milan, Italy; 5Dipartimento di Medicina d’Urgenza, IRCCS Fondazione Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy; 6Infectious Diseases, Internal Medicine Department, Providence Hospital, Washington, DC, United States

Background: Biometers - C-reactive protein (CRP) and procalcitonin (PCT) - in community-acquired pneumonia (CAP) could be useful to distinguish bacterial or viral etiology.

Objective: To analyse initial levels of PCT and CPR in hospitalised CAP according to etiological diagnosis.

Material and methods: Prospective observational study in 685 patients. The etiology of CAP was classified as bacterial, viral and atypical (Mycoplasma, Chlamydia, Chlamydia trachomatis and Chlamydia pneumoniae). We have calculated the cut-off points of PCT and CRP to differentiate bacterial or viral etiology and its diagnostic value through sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV).

Results: An etiological diagnosis was reached in 295 (43%) patients: 203 (29.6%) bacterial - 118 S pneumoniae (51.1%) and 24 Legionella (11.8%), 12 (1.8%) virus and bacteria (2.3%) and 24 (3.5%) atypical. The comparison between Legionella vs S pneumoniae with a cut off PCT ≥ 2 and S:70%; E:59%; PPV:27%. NPP:90%. Atypical or Bacteria with a threshold of PCT ≥ 0.5 and S:89%; E:68%; PPV:22%. NPV:97%. Viruses vs Bacteria with a cut off PCT < 0.5 and S:8.9%; E:6%. PPV:12%. NPV:99%.

Biomarkers and etiological diagnosis CAP

<table>
<thead>
<tr>
<th>Atypical vs Bacteria</th>
<th>Virus vs Bacteria</th>
<th>Virus vs Atypical</th>
<th>Legionella vs S pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>PCT</td>
<td>PCT</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>11.3 vs 19, p=0.92</td>
<td>12 vs 19, p=0.67</td>
<td>12 vs 11.3, p=0.73</td>
<td>24.9 vs 19.9, p=0.009</td>
</tr>
<tr>
<td>PCT 0.19 vs 1.12, p=0.0001</td>
<td>0.24 vs 1.12, p=0.005</td>
<td>0.24 vs 1.12, p=0.73</td>
<td>0.7 vs 1.7, p=0.40</td>
</tr>
</tbody>
</table>

The results expressed in medians.

Conclusion: A threshold of PCT ≥ 0.5 rules out viral etiology with a very high negative predictive value. Legionella is associated with initial higher CRP. CPR and PCT do not allow to differentiate between viral or atypical etiology.
The aim of our study was to evaluate the impact of the inflammatory response on admission and time to reach clinical stability (TCS) in hospitalized patients with CAP. An observational, prospective study was performed on consecutive patients hospitalised for CAP from April to December 2010 at the Respiratory Dept., Policlinico Hospital, Milan, Italy. Cytokines were detected on blood samples collected within 24 hours from the admission with a high sensitivity immunoassay, and were classified as pro-inflammatory (IL6) and anti-inflammatory (IL4 and IL10). Gradients between the latter and the former were also calculated. Two groups of patients were identified: those who reached CS within 3 days from the admission (Group A) and the rest of the population (Group B).

A total of 43 subjects were prospectively enrolled (26 males; mean±SD age: 71±18 yrs). Cytokine values are shown in Table according to the two study groups.

<table>
<thead>
<tr>
<th>Cytokine, pg/mL</th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>20.51±25.93</td>
<td>142.32±164.29</td>
<td>0.015</td>
</tr>
<tr>
<td>IL4/IL6</td>
<td>0.28±0.45</td>
<td>0.05±0.07</td>
<td>0.006</td>
</tr>
<tr>
<td>IL10/IL6</td>
<td>0.13±0.11</td>
<td>0.04±0.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Negative correlations were found between IL10/IL6 ratio and TCS (r = -0.372, p=0.014), as well as IL4/IL6 ratio and TCS (r = -0.312, p=0.042). An effective anti-inflammatory response seems to be a protective factor, whilst individuals showing unbalanced pro-inflammatory patterns take a longer time to recover. Further research is needed to assess the potential application of specific therapeutic agents in order to attenuate inflammatory damage.

**P1465** Biomarkers and community acquired pneumonia (CAP) severity

Ana Lasierra1, Sergio Fandos1, Elisa Mincholé1, Ana Lilian Simon1, Maria Angeles Ruiz2, David Nieto1, Elena Forcén1, Salvador Bello1. 1Pulmonology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain; 2Clinical Biochemistry Department, Hospital Universitario Miguel Servet, Zaragoza, Spain; 3Microbiology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain

To check if any biomarker can be useful to assess Community Acquired Pneumonia (CAP) severity, we studied white blood cells count (WBC), and levels of C Reactive Protein (CRP), Procalcitonin (PCT) and Proudenomedullin (MR-proADM), as well as PSI and CURB65 scores from 228 patients with CAP within the first 24 hours of their admission in our hospital.

MR-proADM correlated better with both severity scores than other biomarkers, and was the only biomarker able to distinguish among all different risk classes of PSI score (p<0.05 for every of the two groups comparisons, see figure 1 and 2). ROC analysis for discrimination between low risk (PSI 1-3) from high risk (PSI 4-5) CAP showed that MR-proADM had the best AUC (0.811) and could be considered a good predictor of CAP severity (see figure 1 and table 1). Optimal cut-off of MR-proADM of 0.646 mmol/L showed a sensitivity of 92.1%, specificity 55.1%, positive predictive value 76.2%, and negative predictive value 80.3% for severe CAP.

**MR-proADM can be helpful, together with validated clinical scores, to identify CAP severity in the first hours of patient’s management.**

**P1466** Biomarkers to discriminate bacterial, viral and mixed community acquired pneumonia (CAP)

Elsa Mincholé1, Ana Lasierra2, Ana Lilian Simon1, Sergio Fandos1, Maria Angeles Ruiz2, Virginia Moya1, Francisco De Pablo1, Salvador Bello3. 1Pulmonology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain; 2Clinical Biochemistry Department, Hospital Universitario Miguel Servet, Zaragoza, Spain; 3Microbiology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain

To find out if C Reactive Protein (CRP), Procalcitonin (PCT) and Proudenomedulin (Pro-ADM) are able to discriminate different CAP etiologies, we collected biological samples from 228 patients admitted in our hospital with CAP in the first 24 hours. Average age: 73 years, 61% males. We performed a complete microbiological searching, and found at least one pathogen in 155 (67.98%) patients. Fifty seven were typical bacterial CAP, 57 viral or atypical 41 were mixed (virus + bacteria).

**Results:**

- **PCT** was the only biomarker that showed significant differences (p<0.0001) between typical bacterial CAP (2.402 ng/mL) and viral/atypical bacterial CAP (0.272 ng/mL). Also, was the only biomarker that discriminated (p=0.007) viral pneumonia from mixed pneumonia (1.568 ng/mL).
- **PCT** and CRP levels in viral CAP showed significant differences (p<0.0001 and p=0.046 respectively) when compared to the other etiologies grouped together (typical bacterial + mixed).
- **A PCT cut-off of 0.255 ng/mL identified typical bacterial involved CAP (bacterial and mixed) from viral/atypical ones, with a sensitivity of 74.23% and a specificity of 50%.

**Conclusion:** CRP, and especially PCT, seem to be useful in early identification of typical bacteria-involved CAP, including those in association with viruses.

**P1467** The ability of pro adrenomedullin to predict severe sepsis in patients with community-acquired pneumonia

Ane Uranga1, Pedro Pablo España1, Alberto Capelastegui1, Inmaculada Gorordo1, Rosa Díez1, Amaia Bilbao2, Carmen Mar3, Edurne Bereciartu4, Edurce Bereciartu5. 1Pneumology, Hospital of Galdakao, Galdakao, Vizcaya, Spain; 2Basque Foundation for Health Innovation and Research, Basque Foundation for Health Innovation and Research, Sondeka, Vizcaya, Spain; 3Biochemistry, Hospital of Galdakao, Galdakao, Vizcaya, Spain; 4Microbiology, Hospital of Galdakao, Galdakao, Vizcaya, Spain

**Objective:** The aim of this study was to compare the ability that validated predictive rules (PSI and CURB65) and the new biomarker Pro adrenomedullin (proADM), had to predict severe sepsis.

**Methods:** We prospectively included patients over 18 years old for a period of one year. PSI and CURB65 scores were estimated to all of them on admission. Blood samples were collected at the time of diagnosis to determine proADM
Results: 685 patients were included: 40 of them with bacteremia. The medians of CRP, PCT, TNF-α and IL-6 were significantly higher in those with bacteremia (Table 1). PCT ≥36 to predict positive blood cultures showed sensitivity (S) of 85%, specificity (E) 42% and negative predictive value (NIVP) of 98% (ROC area 0.70). The threshold of IL-6 ≥ 150 for predicting bacteremic CAP showed: 60% sensitivity, 70% and 96% negative predictive value (ROC area 0.65).

Conclusions: Bacteremic CAP is associated with higher inflammatory cytokines systemic. PCT showed the highest diagnostic value. A cutoff ≥0.36 has high sensitivity. Lower initial PCT levels rule out bacteremic CAP with a high negative predictive value.

P1470

C-reactive protein (CRP) utility in severe community-acquired pneumonia (SCAP) prognosis

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Background: Among SCAP patients mortality is usually high, especially in those requiring invasive mechanical ventilation (IMV) or vasopressor support (VS). We aimed to assess CRP on admission and 6th day values association with mortality and adverse outcomes in SCAP patients requiring intensive care unit (ICU) admission.

Methods: 30 ICU patients with SCAP (CURB-65 class 3,4) were enrolled. Control group included 16 healthy volunteers. X-ray examination, CRP levels measurement were performed on admission and on day 8. The main endpoints were in-hospital outcomes (in-hospital mortality (IH), duration of ICU stay (DICUS), necessity of IMV and VS). Results: CRP values correlated with CURB-65 score (p=0.8, p<0.05 and r=0.76; p<0.05 respectively) and were statistically different in CURB-65 class 3 and 4 patients (p<0.05). CRP levels were higher in non-survivors vs survivors [median] [311 vs 24mg/ml, p<0.05 respectively] on the 1st and 8th days [249 vs 89 mg/ml, p<0.05 respectively], revealed correlation with IHM (r=0.64, p<0.05 and r=0.6; p<0.05 respectively). Longer DICUS was associated with higher CRP values on admission (r=0.43, p<0.05). CRP on the 1st day correlated with necessity of VS and IMV (r=0.79; p<0.05 and r=0.63; p<0.05 respectively), their values appeared to be higher in patients requiring VS and IMV vs those who didn’t need them [311 vs 244 mg/ml respectively, p<0.05]. Negative X-ray dynamics was associated with increased CRP levels on the 1st day (r=0.55; p<0.05).

Conclusions: Increased CRP values in SCAP patients requiring ICU admission are associated with disease severity, negative X-ray dynamics and could be used for identifying patients with high IHM risk, prediction of DICUS, necessity of VS and IMV.

P1471

Biomarkers in severe community-acquired pneumonia (SCAP) prognosis, complications and outcomes

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Background: Early prognostic assessment is crucial for SCAP patients management. We studied accuracy of C-reactive protein (CRP), interleukin-2 (IL-2), interferon-γ (INF-γ), free triiodothyronine (T3), free tetraiodothyronine (T4), thyroid stimulating hormone (TSH), total cortisol (TC) in predicting SCAP hospital mortality and disease severity, outcomes, complications, need for invasive mechanical ventilation (IMV) and vasopressor support (VS).

Methods: 30 ICU patients with SCAP CURB-65 class 3-5 were enrolled. Control group included 16 healthy subjects. X-ray examination, serum markers measurement were performed on the 1st day after admission.

Results: CAP severity was associated with enhanced CRP (r=0.8, p<0.05), IL-2 (r=0.64; p<0.05), TC (r=0.87; p<0.01), decreased T3 (r=-0.75; p<0.05) values. Non-survivors revealed higher CRP/L-2, TC, lower T3, TSH levels vs those in survivors [median: 11 vs 24mg/ml, p<0.05], [138 vs 8.9 pmol/l, p=0.03], [1377 vs 865 pmol/l, p=0.03], [2.8 vs 4.6 pmol/l, p<0.05], [0.89 vs 2.6 nmol/l, p=0.03]. Necrotising pneumonia developed in patients with decreased IL-2, T4 values (r=0.6, p=0.04 and r=0.48, p=0.03) pleural effusion - in those with enhanced INF-γ levels (r=0.8, p=0.01). IL-2/CRP/Tc values were higher in patients requiring VS [122 vs 19 pg/ml, p=0.04], [311 vs 232 mg/ml, p=0.05], [1377 vs 865 pmol/l, p=0.03]. Enhanced CRP, low T3 levels were associated with IMV requirement (r=0.63; p<0.05 and r=0.71; p<0.05). Duration of ICU stay correlated with TC, CRP values (r=0.89; p=0.01 and r=0.43; p=0.04) length of hospitalisation - with TSH, T4 (r levels 0.56, p=0.01 and r=0.14, p=0.05).

Conclusions: CRP, thyroid hormone, TC, IL-2, INF-γ can augment early prognostic assessment of SCAP pts.
Comparison of inflammatory response biomarkers to predict complications in hospitalized patients with community-acquired pneumonia

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Background: Recently, an extensive research has gone into identifying the predictive value of biomarkers for complications in community-acquired pneumonia (CAP).

Objective: The aim of this study was to evaluate the utility of inflammatory biomarkers measured on admission in hospitalized patients with CAP.

Methods: We prospectively included patients over 18 years old for a period of one year. Procalcitonin (PCT), C reactive protein (CRP) and Pro adrenomedullin (ProADM) were compared in predicting complications occurred in the follow-up of 30 days. Mortality, severe sepsis, ventilation and/or septic shock and ICU/ICU admission were the complications analyzed. For the comparison of biomarkers, the nonparametric Wilcoxon test was used, whereas AUC was used to measure the predictive ability of each biomarker.

Results: A total of 320 patients with diagnosis of CAP were included in our study and samples for biomarkers could be extracted in 258 of them. Table 1 shows the results of the comparison of the biomarkers according to each outcome, and the AUC values. Biomarkers are described as median and interquartile range.

Conclusions: ProADM is a powerful tool for the prediction of mortality and other complications in hospitalized patients with CAP. In addition, we found that PCT has the greatest predictive value for complications such as ventilation/shock or ICU/ICU admission.

P1474 Interleukin-2 (IL-2) and Interferon-γ (IFN-γ) in identifying severe community-acquired pneumonia (SCAP): clinical outcomes and complications

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Background: Exaggerated and protracted proinflammatory response is associated with poor prognostic implications in SCAP. We assessed the diagnostic value of IL-2 and IFN-γ in identifying SCAP-in-hospital outcomes and complications.

Methods: 30 SCAP patients CURB-65 class 3-4 were enrolled. Control group included 16 comparable healthy volunteers. We performed X-ray examination, IL-2 and IFN-γ measurement within the first 24 hours after admission and on day 8. In hospital mortality (IHM), need for vasopressor support (VS), SCAP complications (necrotising pneumonia (NP), pleural effusion (PE)) were analyzed.

Results: Increasing CAP severity was associated with increased IL-2 values both on the 1st day (r=0,64; p<0,05).IL-2 on admission values correlated with IHM (r=0,67; p<0,05). Patients with poor clinical prognosis had higher IL-2 levels on the 1st day vs those who survived [median]138 vs 20,8 pg/ml, p<0,05 respectively]. IL-2 on admission correlated with need for VS (r=0,65; p<0,05) and revealed higher concentrations in patients requiring VS vs those with stable haemodynamics [122 vs 19pg/ml, p=0,05]. Patients who developed NP showed lower IL-2 levels vs those without destructive lung changes [16 vs 26 pg/ml, p<0,05]. PE in SCAP patients correlated with enhanced IFN-γ levels on the 1st and 8th days (r=0,8; p<0,01 and r=0,69; p=0,02). Patients with PE demonstrated higher IFN-γ values [41 and 20 pg/ml, p=0,031] vs those without PE [0,3 and 3,8 pg/ml, p<0,05].

Conclusions: IL-2 on admission values are reliable for mortality risk stratification, prediction of need for VS and NP development, IFN-γ could be helpful in identifying PE complication in SCAP patients.

P1475 Thyroid hormones implication in severe community-acquired pneumonia (SCAP): Relationship with survival, outcomes and clinical complications

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Background: The low thyroid hormone levels in the absence of primary thyroid disease have proved to be predictive of outcomes and disease severity in critical illness. We aimed to assess thyroid function in SCAP patients requiring intensive care unit (ICU) admission and it’s association with in-hospital outcomes, SCAP complications, need for invasive mechanical ventilation (IMV) and vasopressor support.

Methods: 40 ICU patients with SCAP CURB-65 class 3-5 were enrolled. Control group included 16 healthy subjects. X-ray examination, free triiodothyronine (T3), free tetraiodothyronine (T4), thyrotropin (TSH) levels were compared in predicting complications occurred in the follow-up (necrotising pneumonia (NP), pleural effusion (PE)) were analyzed.

Results: FT3 initial values decreased with increasing severity of CAP (r=0,75; p<0,0007). FT3 and TSH levels were lower in non-survivors vs in survivors [median]138 vs 20,8 pg/ml, p<0,05 respectively]. IF-γ levels on admission were higher in non-survivors vs those with stable haemodynamics [122 vs 19pg/ml, p=0,05]. Patients who developed NP showed lower IL-2 levels vs those without destructive lung changes [16 vs 26 pg/ml, p<0,05]. PE in SCAP patients correlated with enhanced IFN-γ levels on the 1st and 8th days (r=0,8; p<0,01 and r=0,69; p=0,02). Patients with PE demonstrated higher IFN-γ values [41 and 20 pg/ml, p=0,031] vs those without PE [0,3 and 3,8 pg/ml, p<0,05].

Conclusions: Thyroid hormone levels in SCAP patients are reliable markers of diseases severity, high risk of IHM and NP development and can be helpful in identifying patients requiring IMV and predicting length of in-hospital stay.

P1476 Pro-adrenomedullin, procalcitonin and CRP levels to predict bacterial pneumonia in patients admitted to emergency room

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Objectives: To assess if MR-proADM, PCT and CRP levels can distinguish
bacterial pneumonia from other kind of lower respiratory tract infections (LRTI).

Methods: Patients with fever and respiratory symptoms that were admitted in emergency room (ER) and from whom blood cultures were drawn. After retrospective analysis, patients were classified as: pneumonia (n=85), chronic obstructive pulmonary disease (COPD) exacerbation (n=25) and bronchial infection (n=52). Four patients were admitted to ICU and 9 died.

Results: PCT showed significantly higher levels in pneumonia when comparing with COPD exacerbation (p=0.003) and bronchial infection (p=0.002). CRP only showed significantly higher levels when comparing pneumonia group vs bronchial infection (p=0.002). Finally, MR-proADM showed statistically higher levels when comparing pneumonia group with COPD exacerbation (p=0.014) and bronchial infection (p=0.006). PCT and MR-proADM showed significantly higher levels in cases of definite bacterial diagnosis in comparison to other diseases (p-value < 0.001). PCT and MR-proADM are significantly higher in patients admitted to ICU (p=0.011 and p=0.001). Regarding mortality, no significant differences were found.

Conclusions: PCT and MR-proADM show significantly higher levels in pneumonia in comparison to other lower respiratory tract infections. PCT and MR-proADM levels are increased in confirmed bacterial infections. Biomarkers measurement can be helpful for the management of patients admitted in ER with clinical symptoms of respiratory tract infection.

160. Progress in pathology of lung cancer

P1477

LSC 2011 Abstract: Molecular interplay between inflammation and occurrence of proliferation: Role of cadmium

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Introduction: Cadmium is one of the inflammation-related xenobiotics with potent carcinogenicity. The mechanism between inflammation and cell proliferation due to chronic cadmium exposure has not been studied yet (Lau KT, et al., Toxicol Appl Pharmacol 2006).

Objectives: The present study was undertaken to determine molecular mechanism of inflammation linked cell proliferation due to cadmium exposure in mice and lung cancer cell line.

Methods: Swiss albino mice and A549 cell line were chosen for experiments. Levels of different cytokines, expression level of cell cycle regulatory proteins estimated by ELISA, western blot and immunoprecipitation. Other techniques used scanning electron microscopy, histopathology and Cytotoxic assay. Cell cycle analysis, DNA fragmentation assay and RT-PCR experiments.

Results: Prolonged exposure of low concentration of cadmium resulted in up regulation of proinflammatory cytokines and cell cycle regulatory molecules both in vivo and in vitro. Swiss albino mice (n=9, 30 ppm of CdCl2 for 90 days) and A549 NSCLC cell line (n=6) were treated with 1 µM and 10 µM of cadmium chloride respectively. Levels of inflammatory cytokines TNF-alpha, IL-6 and IL-8 were significantly higher in cadmium treated mice and cells. Levels of cell cycle regulatory proteins cyclin D1 and cyclin E were also higher in treated samples.

Conclusion: Cadmium promotes inflammation and cell proliferation in vivo and in vitro due to cadmium toxicity.

P1478

LSC 2011 Abstract: Cigarette smoke-induced inflammation promotes melanoma cell metastasis in lung parenchyma

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It is only during the last decade that clear evidence has been obtained that inflammation plays a critical role in different stages of tumor development, including initiation, promotion, malignant conversion, invasion and metastasis. There is increasing evidence that an inflammatory microenvironment is an essential component of all tumors (Paula and Lyden, Nat Rev Cancer, 2009 Apr;9(4):283-93). In the present study, we assessed in vivo the impact of cigarette smoke (CS) on the tumor cell extravasation in lungs after tail vein injection of B16F10 melanoma cells. We first characterized airway inflammation obtained after smoke exposure (reference smokers 3R4F) for varied time periods (1, 2, 4, 8 and 12 weeks). Smoke exposure was performed 5 days a week. Neutrophils, alveolar macrophages, interstitial macrophages, dendritic cells, T cells and natural killer T (NKT) cells, were characterized in lung tissues of mice exposed to CS and AIR using flow cytometry. In vivo, the direct effect of cigarette smoke extract (CSE) on proliferation of B16F10 melanoma cells was determined for 1 to 5 days. In vitro, mice exposed for 2 weeks to cigarette smoke or air were injected with B16F10 melanoma cells in the tail vein. After 3 weeks, hematoxylin-eosin staining allowed quantification of lung metastasis (tumor area/totul lung area). An increase of metastasis and implantation site in lungs was observed in CS exposed group. Conceivably, CS constitutes significantly promote extravasation of melanoma cells in lung tissues. The mechanism or signaling pathway responsible for this dissemination needs to be further investigated.

P1479

SK-216, an inhibitor of plasminogen activator inhibitor-1, limits tumor growth and lung metastasis formation probably through the reduction of tumor angiogenesis

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Introduction: Plasminogen activator inhibitor-1 (PAI-1), the main inhibitor of plasminogen activators, is known to be involved in tumor progression.

Objectives: To investigate whether a PAI-1 inhibitor, SK-216, can limit tumor growth and lung metastasis formation.

Methods: C57BL/6 mice were subcutaneously inoculated with Lewis lung carcinoma (LLC) cells and tumor volume (mm3) was measured twice a week until 2 weeks after the inoculation. The numbers of lung tumors were also counted 21 days after the injection of LLC cells through the tail vein. The mice were given either water or SK-216 (500 p.p.m.) in drinking water. In addition, the sections of tumor were stained with CD31 antibody, and the number of CD31-positive vessels was counted in three random microscopic fields per section.

Results: The volumes of subcutaneous tumors 14 days after the inoculation of LLC cells were significantly smaller in SK-216-treated group than those in control group (mean ± SD, 1566±515.9 mm3 and 2235±353.0 mm3, respectively; p<0.01). The numbers of lung surface tumors were significantly lower in SK-216-treated group than those in control group (3.3±4.1 and 12.1±7.3, respectively; p<0.02). The numbers of CD31-positive vessels in subcutaneous or lung tumor sections were statistically significantly lower in SK-216-treated group (60.5±15.9/field and 78.7±21.8/field, respectively; p<0.004: lung tumor; 24.0±7.9/field and 44.8±4.4/field, respectively; p<0.002).

Conclusion: These results suggest that SK-216 limits tumor growth and lung metastasis formation probably through the reduction of tumor angiogenesis.

P1480

The long non-coding MALAT-1 RNA indicates a poor prognosis in NSCLC and induces migration and tumor growth

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Introduction: The functions of large long non-coding RNAs (lncRNA) have remained elusive in many cases. MALAT-1 (Metastasis-Associated-in-Lung-Adenocarcinoma-Transcript-1) is a lncRNA, that is highly expressed in several tumor types.

Methods: Overexpression and RNA interference (RNAi) approaches were used for the analysis of the biological functions of MALAT-1 RNA. Tumor growth was studied in nude mice. For prognostic analysis MALAT-1 RNA was detected on paraffin embedded lung cancer tissue probes (n=352) using in-situ hybridization.

Results: MALAT-1 was highly expressed in several human non-small cell lung cancer cell lines. MALAT-1 expression was regulated by an endogenous negative feedback loop. In A549 NSCLC cells, RNAi mediated suppression of MALAT-1 RNA suppressed migration and clonogenic growth. Forced expression of MALAT-1 in NIH 3T3 cells significantly increased migration. Upon injection into nude mice, NSCLC xenografts with decreased MALAT-1 expression were impaired in tumor formation and growth. In-situ hybridization on paraffin embedded lung cancer tissue probes revealed that high MALAT-1 RNA expression in squamous cell carcinoma of the lung was associated with a poor prognosis.

Conclusion: These data indicate that MALAT-1 expression levels are associated with patient survival and identify tumor promoting functions of MALAT-1.

P1481

Expression of miR-126 and miR-126′ in primary tumors and metastasis of adenocarcinoma and squamous carcinoma of the lung

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MicroRNAs are a family of small non-coding RNAs that negatively regulate gene expression at post-transcriptional level. Their expression has been proved to be associated to cancer but several aspects of this association remain elusive.
miR-126 and miR-126* are processed from the same precursor microRNA and are down-regulated in non-small cell lung cancer (NSCLC). However, information is lacking regarding their involvement in metastatic potential and differential expression in adenocarcinoma and squamous carcinoma of the lung. In this study, these questions were approached by comparing microRNA levels in 37 samples of matched adjacent lung parenchyma, primary tumour and lymph node metastasis (when present). Each kind of tissue was isolated by laser microdissection and, after RNA extraction, the two microRNAs were quantified by RT-qPCR. Both miR-126 and miR-126* were found to be down-regulated in primary tumour cells comparatively to matched normal tissue (p-value<0.001). On the contrary, no significant differences were found between primary tumour and lymph node metastasis cells or between tumour cells of metastatic and non-metastatic samples. Although overall expression was similar in adenocarcinoma and squamous carcinoma, in non-metastatic tumors miR-126 and miR-126* expression was lower in squamous carcinoma (p-value=0.037 and p-value=0.035, respectively). These results suggest that these microRNAs might act as tumor suppressors but are not involved in the metastatic process. In addition, their expression seems to relate to the type of NSCLC in non-metastatic tumors and might therefore be useful for their characterization.

P1482
Expression and significance of VE-cadherin and E-cadherin in non-small cell lung cancer
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Objective: The aims of our study were to assess the expression of vascular endothelial cadherin (VE-cadherin) and epithelial cadherin (E-cadherin) in human non-small cell lung cancer (NSCLC) tissues and to correlate these expression levels with clinicopathological characteristics of NSCLC.

Methods: The expression levels of VE-cadherin and E-cadherin were examined by immunohistochemistry in NSCLC tissues from 39 patients and in 30 adjacent non-neoplastic tissues that were at least 5 cm away from the tumor tissues.

Results: The positive rates of VE-cadherin and E-cadherin in NSCLC were 51.3% (20/39) and 43.6% (17/39), respectively. The positive rate of E-cadherin in NSCLC was lower than in adjacent non-neoplastic tissues (73.3,22/30, P<0.05). The VE-cadherin expression level inversely correlated with lymph node metastasis (P<0.05).

Conclusions: We demonstrated the aberrant expression of VE-cadherin in NSCLC and the downregulation of E-cadherin expression. Both of these proteins are associated with lymph node metastasis. These results indicate that both of these proteins may take part in the growth and metastasis of NSCLC and thus may be therapeutic targets for the treatment of NSCLC.

P1483
Transcriptional regulation of the human osteopontin promoter in non-small cell lung cancer
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Background: Elevated osteopontin (OPN) transcription often correlates with increased metastatic potential of transformed cells, and OPN has been shown to enhance metastatic ability. We hypothesized that transcription determines OPN expression, tried to find out response element resided in the DNA sequence element and suppression molecules.

Methods: We investigated the transcriptional regulation of OPN in non-small cell lung cancer cell lines. These elements were treated with pp2 (src tyrosine kinase inhibitor), FTI (Farnesyl transferase inhibitor), and 2BP (2 bromo palmitate) in order that confirm suppress transcriptional expression.

Results: Deletion and mutagenesis analyses of the OPN promoter region identified a proximal promoter element (–123 to –89) relative to the transcription initiation site) that is essential for maintaining high level of OPN expression in the tumor cells. Proximal promoter elements (–123 and –89) were treated with pp2, FTI and 2BP, whether if transcriptional expression could be suppressed by these molecules. In case of FTI, OPN expression was suppressed, but statistical significance wasn’t meaningful.

Conclusion: The proximal promoter element (–123 to –89) was essential for maintaining high level of OPN expression in non-small cell lung cancer cell lines. Further investigation for searching material to suppress OPN expression is needed.

Inhibitor of DNA-binding (Id) – 1 and 3 proteins overexpression has impact on prognosis of lung adenocarcinoma
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The inhibitor of DNA-binding (Id) are involved in cell cycle regulation, apoptosis and angiogenesis. Many authors suggest participation of Id genes in development and progression of large number of human cancer, but their role in lung cancer has not been evaluated.

Objectives: To evaluate Id 1, 2 and 3 expressions in lung adenocarcinoma in correlation to age and survival.

Methods: Ids were quantified in tumoral and non-tumoral tissues from 43 patients who underwent lobectomy for lung adenocarcinoma. Their preoperative clinical stages were $T_1$-$N_0$-$M_0$ and the mean follow-up was 26.7 months. Immunohistochemistry was applied to analyze the intensity of Ids expression in nucleus and cytoplasm (quantitative scores performed in 500 cells). The impact of these markers was tested on follow-up until death from recurrent lung cancer.

Results: Distinct profile of Ids expression was observed between tumoral and the matched adjacent nonmalignant tissue. Ids were significantly more expressed in tumoral cells. Patients whose tumor cells expressed lower scores of cytoplasm Ids tended to present better long-term survival (p=0.05). The Cox model controlled for age, gender and type of NSCLC.
P1487

Adenovirus-mediated AP-2α down-regulates MnSOD expression in lung cancer A549 cells and its molecular mechanism
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Objective: MnSOD is potential therapy target for lung cancer and it is important to control MnSOD aberrant expression in lung cancer cells. In this study, we investigate the effect of AP-2α activation on MnSOD expression in lung cancer cell line and provide experimental evidence on the applications of AP-2 for lung cancer therapy.

Methods: A549 cells were transfected with the Adenovirus-AP-2α construct (AD-AP-2α) at multiplicities of infection (MOI) of 0, 10, 30, 50 MOI or with the adenovirus-lacZ reporter gene construct (Ad-lacZ). The MOI A549 cells were transfected for 0, 6, 12, 24, 48 hrs with Ad-AP-2α at 50 MOI and also were transfected for 24hrs with the dominant-negative mutant AP-2α construct with liposome-mediated method. The time- and dose-dependent effects of AP-2 on MnSOD expression were detected by RT-PCR and Western blot.

Results: (1) With increasing Ad-AP-2α titers, the expression of MnSOD is decreased. (2) Transfected with 50 MOI Ad-AP-2α and measured expression of MnSOD at 6, 12, 24, 48 hrs, we observed a concomitant decreasing in MnSOD expression. (3) Compared with the controls, the expression of MnSOD was declined after transfecting the dominant-negative mutant AP-2α construct into lung cancer (A549) cells.

Conclusions: The results suggest that AP-2 represses MnSOD expression in lung cancer cells and down-regulation of MnSOD may be related to DNA binding domain of AP-2α.

P1488

Telomerase (h-TERT) and targeting EGFR in non small cell lung carcinoma: A combined immunohistochemistry and chromogenic in situ hybridization study based on tissue microarrays
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Purpose: Our aim was the evaluation of EGFR gene and protein alterations in NSCLC and the potential role of telomerase in the regulation of its expression.

Methods: Using tissue microarray technology, forty (n=40) paraffin embedded histologically confirmed primary NSCLCs were cored twice at a diameter of 1mm and re-embedded into a recipient block. Immunohistochemistry was performed by the use of monoclonal antibodies anti-EGFR (31G7), and anti-telomerase/h-TERT (4F12). Also, a Chromogen in situ hybridization protocol was applied based on the use of EGFR gene and chromosome 7 centromeric probes. Computerized Image Analysis was performed for the evaluation of immunohistochemistry results.

Results: EGFR overexpression was observed in 23/40 (57.5%) cases correlating to stage (p=0.001) and histological type (p=0.04). Telomerase was overexpressed in all examined cases (high and moderate levels) correlating to stage (p=0.001). A significant value of concordance (kappa=0.686, 0.677±0.695) was assessed comparing telomerase and EGFR protein expression. EGFR gene amplification was identified in 2/40 (5%) cases associating to histological type (p=0.027) and chromosome 7 aneuscopy in 7/40 (17.5%) cases.

Conclusions: NSCLC is characterized by rare cases of EGFR gene amplification and this genetic event may affect the efficacy of targeted therapeutic strategies based on monoclonal antibodies. Also, the strong concordance between EGFR and this genetic event maybe affect the efficacy of targeted therapeutic strategies based on monoclonal antibodies.

P1489

Inhibition of B7-H4 gene expression by RNA interference (RNAi) in lung cancer A549 cell line
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Background: B7-H4, a member of the B7 family, is involved in the regulation of antigen-specific immune responses. Here we addressed its expression in non-small-cell lung cancer (NSCLC) pathology and correlation to the number of CD3+ tumor infiltrating T-lymphocytes in invasive carcinomas. We also observe the effects of B7-H4 gene expression on cell proliferation and migration in the human NSCLC cell line.

Methods: B7-H4 expression was evaluated by immunohistochemistry in 102 patients with NSCLC who underwent surgical tumor resection. Expression data was correlated with clinicopathologic features and with the number of tumor-infiltrating T-cell. B7-H4 mRNA was cloned into pGCU6Neo plasmid and the product was transfected into A549 cells with Lipofectamine 2000.

Results: B7-H4 is transcribed in three cell lines. In tumor tissues, expression of B7-H4 in A549 is both in the cell membrane and in the cytoplasma of B7-H4 transfection vector-pGCaB7-H4 was successfully constructed. After transfected with pGC SHB7-H4, the expression of B7-H4mRNA in A549 cells was obviously decreased with an increased cell proliferation observably. Compared to cell lines without treatment, the proliferation of cell lines cultivated with decreased B7-H4 gene was increased, the cell cycle was blocked in the G0 as well, invasion and mobility abilities of cells in vitro were added.

Conclusion: Our observations also suggest that the B7-H4 gene is associated with A549 cell proliferation, migration and cell cycle distribution. RNAi recombinant of B7-H4 gene could effectively inhibit the expression of B7-H4 mRNA in A549 cells.

P1490

Novel functions of stanniocalcin-1 (STC1) through uncoupling protein 2 (UCP2) up-regulation: promoting survival of cancer cells under oxidative stress and inducing the uncoupling respiration (Warburg effect)
Shinya Okkuchi, Toshiaki Kakoki, Masahito Ehima, Toshiharu Nawai. Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

We have demonstrated that multipotent stromal cells (MSCs) promote cell survival though upregulation and secretion of stanniocalcin-1 (STC1) (Stem Cells 2009; 27: 670-81). This study demonstrates that MSC derived STC1 promotes survival of lung cancer A549 cells through the uncoupling of oxidative phosphorylation, the reduction of intracellular reactive oxygen species (ROS) and concomitant shift towards a more glycolytic and more oxygen consuming metabolic profile (known as the Uncoupling Respiration). MSC-derived STC1 upregulated uncoupling protein 2 (UCP2) in injured A549s in an STC1 dependent manner. Knock down of UCP2 reduced the ability of MSCs to reduce cell death in the A549 population.

Our data suggest that MSCs promote cell survival by regulating the uncoupling respiration in an STC1 dependent manner. Furthermore, STC1 may provide promising avenues for treatment of reactive oxygen species and metabolic disorders.

P1491

TNF neutralization ameliorates urethane-induced lung carcinogenesis
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Aim: To preclinically investigate the therapeutic potential of TNF blockade against lung neocarcinosis (TNF in the lung).

Methods: Long-term studies: Balb/c mice received urethane or saline followed by anti-TNFα or placebo during weeks 0-4 (early), 20-24 (late), or 0-32 (continuous) post-urethane. End-points were lung tumor number (and) diameter (δ) at 32 weeks. Short-term studies: Balb/c mice received weekly doses of infliximab 15 mg/kg, Amgen-Wyeth; 10 mg/kg) during weeks 0-4 (early), 20-24 (late), or 0-32 (continuous) post-urethane. End-points were lung tumor number (and) diameter (δ) at 7 days.

Results: Compared with controls (δ=16.2±1.6 δ=1.0±0.07mm), early sTNFRFc-treated mice had fewer lung tumors of equal size (p=0.01; 1.3, P<0.05; b=1.07±0.03mm, P>0.05), but late sTNFRFc-treated mice had equal numbers of smaller lung tumors (b=14.1±1.2, P>0.05; δ=7.1±0.07mm, P>0.01). Continuous sTNFRFc resulted in reduced lung tumor number and size (b=9.3±1.0, P<0.05; δ=7.6±0.03mm, P>0.05). sTNFRFc-treated mice had fewer macrophages, but higher IFN-γ and IL-10 levels in BAL; tumors from these mice showed slower proliferation and angiogenesis. In short-term studies, sTNFRFc inhibited urethane-induced macrophage influx and TNF expression, but enhanced IFN-γ and IL-10 expression in BAL. A possible source of IFN-γ and IL-10 in sTNFRFc-treated mice were macrophages, which responded to sTNFRFc by enhanced IFN-γ and IL-10 expression.
Conclusion: TNF blockade halts lung tumorigenesis in mice, and may be useful in lung cancer chemoprevention.


P1492
Krebgs von den Lungen-6 (KL-6) is a prognostic biomarker in patients with surgically resected non-small cell lung cancer
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Background: By immunizing mice with a lung adenocarcinoma cell line, we previously established a murine IgG1 monoclonal antibody that recognizes a sialylated sugar chain designated Krebs von den Lungen-6 (KL-6). KL-6 is a high-molecular-weight glycoprotein classified as a human MUC1 mucin. The aim of this study was to determine whether KL-6 expression in tumors correlates with circulating KL-6 levels and whether circulating KL-6 has any prognostic value in patients with surgically resected non-small cell lung cancer (NSCLC).

Method: Immunohistochemical analysis of KL-6 expression was performed on 103 NSCLC tissues, and its associations with serum KL-6 levels and survival were examined. We also evaluated whether KL-6 expression patterns and/or serum KL-6 levels could predict prognosis in these NSCLC patients.

Result: Immunohistochemical analysis of KL-6 in NSCLC tissues showed that a depalidized KL-6 expression pattern was associated with a high level of circulating KL-6 and a poor prognosis in NSCLC patients who underwent curative surgery. Furthermore, a high circulating KL-6 level was associated with both poorer progression-free survival (PFS) and overall survival (OS), and multivariate analyses confirmed its independent prognostic value for both PFS and OS (p=0.041 and 0.023, respectively).

Conclusion: Our data suggest that preoperative serum KL-6 level reflects KL-6 expression patterns in NSCLC tissue, and can serve as a useful prognostic biomarker in NSCLC patients who undergo curative surgery.

P1493
Potential therapeutic significance of CIK cells in gefitinib resistant NSCLC with EGFR mutations
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The gefitinib resistant limits its efficacy in the treatment of non-small cell lung cancer (NSCLC), thus, we tried to evaluate the drug-resistance reversal to gefitinib by the cytokine induced killer (CIK) cells. The gefitinib resistant cell line PC-9/GR was developed from a NSCLC cell line PC-9 harboring EGFR E746-A750 deletion by gefitinib selection. The effect of CIK cells alone or combination with gefitinib on PC-9/GR was determined by the cytotoxicity in vitro as well as growth inhibition of NSCLC in vivo. The effects of gefitinib on PC-9/GR cells were compared.

The induction of G0/G1 arrest and apoptosis was observed in PC-9/GR treated with CIK cells in vitro and vivo, however, there was no significant difference in the cytolytic activity of CIK cells against PC-9 and PC-9/GR targets. In addition, a synergistic cytotoxicity was obtained by the combination CIK cells and gefitinib in PC-9/GR through the inhibition of p-ERK and p-AKT activity by CIK cells. Finally, CIK cells inhibition could significantly increase the frequency and function of NK cells and decrease the frequency of Treg cells and level of TGF-β in patients with tumors. In conclusion, CIK cells have a strong cytotoxicity to PC-9/GR and a clinical immune modulation, thus it might be a favorable treatment of NSCLC with EGFR mutations.

P1494
Expression of immunohistochemical markers chromogranin A, Ki-67, CD99, EGRF in resected pulmonary neuroendocrine tumors
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Aims: Recurrent cough (RC) is common in childhood and an important cause of primary care visits. Despite that, data on the natural history of recurrent cough in unselected children are scarce.

Methods: In a population-based cohort in Leicestershire (UK) we measured recurrent cough (defined as chronic night cough + cough apart from colds + GP visits for cough) with repeated questionnaires. For non-wheezers, we computed frequency of recurrent cough at different ages, and determined predictors of RC in multivariative logistic regressions.

Results: We had data on 1247 children aged 1 year, and data on 1127, 1267, 1410, 825 aged 2, 4, 6, and 9 years respectively. Prevalence of RC at these ages was 17%, 19%, 21%, 16% and 12% respectively. Of all children with RC at age 1 year, 62% continued to report RC at age 2 years, and 46%, 35%, 28% at age 4, 6 and 9 years respectively. Factors associated with RC during the first 2 years of life were nursery care and possetting. In contrast, attendance to nursery care in infancy protected from RC at age 6 and 9 years. Associations with family history of atopy were marginal.

Conclusions: Recurrent cough is common and tracks strongly during childhood. At all ages, there are strong associations with upper respiratory symptoms. This might be explained by an increased susceptibility to upper respiratory infections.

P1495
Natural history of recurrent cough in children
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Aims: Many children have asthma-like symptoms in early life, but few develop asthma. Several models for predicting later asthma in symptomatic toddlers have been built, but some included factors that are difficult to assess, and methods used were prone to overfitting, leading to selection or exaggeration of irrelevant factors. We aimed to identify predictors for later asthma avoiding previous limitations.

Methods: In a population-based cohort, we selected 1-3 year-olds with respiratory symptoms (current wheeze or recurrent cough) and related healthcare visits. Asthma (current wheeze or recurrent cough) and related healthcare visits was assessed 5 years (N=1226) and 8 years (N=866) later.

The included factors are easy to assess in clinical practice: family history, symptoms at baseline, demographic and perinatal data. We used lasso penalized logistic

161. Paediatric epidemiology: predicting outcomes of wheeze, antenatal growth, early life exposures and outcome of premature birth

P1496
Robust prediction of later asthma in symptomatic toddlers: A novel approach
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The included factors are easy to assess in clinical practice: family history, symptoms at baseline, demographic and perinatal data. We used lasso penalized logistic
regression to select predictors. This minimizes the number of included predictors while maximizing area under ROC curve (AUC).

Results: Main predictors selected in the model for asthma 5 yrs later (AUC=0.76) were ≥4 wheezing attacks in the past 12 months (OR=1.65), wheeze causing breathlessness (3.1) and activity disturbance (2.4), eczema (1.5) and male sex (1.5). Other predictors (OR<1.5) were: non-viral triggers for wheeze or cough, parental history of asthma and atopy, and low birth weight. The results for asthma 8yrs later (AUC=0.72) were similar.

Conclusion: Among factors easy to assess in symptomatic toddlers, wheeze severity, eczema and male sex are main predictors of asthma in mid-childhood. Because our approach for variable selection avoids overfitting, the resulting prediction models should perform well with new data. However, external validation is needed.

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P1497
Phenotypes of childhood wheeze: Early symptom pattern vs. long term disease course

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Aim: Wheezing in childhood is phenotypically heterogeneous. We investigated how phenotypes defined by early symptom pattern are related to phenotypes based on later retrospective time course.

Method: We analysed data on wheeze-related symptoms (frequency and duration of episodes, shortness of breath (SOB), fever and triggers (chest infection, smoke, cold weather, “other”)) in children from a population based birth cohort (ALSPAC) at ages 6m (n=2261), 18m (2400) and 30m (1786). We used latent class analysis to identify phenotypes, which were compared to previously published phenotypes based on 7 measurements of current wheeze in the first 7yrs of life (Thorax 2008;63:974–980).

Results: We identified 5 phenotypes at age 6m and 6 at ages 18m and 30m. At each age, 3 phenotypes, each comprising 20-30% of children, were identified, one with episodes triggered mainly by infections and cold weather and one with “other” triggers predominating. Other phenotypes were characterised by moderate or mild symptoms and differed in patterns of triggers. Phenotypes were similar at different ages. Among children with mild wheeze, >60% were classified longitudinally as “transient early” or “prolonged early wheezers” while >34%, >46% and >63% of children in the severe groups at ages 6m, 18m, and 30m respectively were classified as “persistent wheezers”.

Conclusion: In children <3yrs from the general population, severe wheeze can be associated both with a viral and a multiple trigger pattern. Severe wheeze in early childhood is a strong predictor of wheeze persisting into school age, regardless of reported triggers.

Funding: European Respiratory Society/Marie Curie Joint Research Fellowship - Number MC 1614-2010.

P1498
Allergic females have the least chance of recovery following early wheezing

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Background: We have previously reported on the outcome in childhood and adolescence in children hospitalized due to wheezing before the age of two. The aim of the present follow-up was to report on the prevalence of and risk factors for asthma at adult age.

Methods: We have prospectively studied asthma development in 101 children hospitalized due to wheezing before the age of two. The cohort was re-investigated 20 years later. We identified 5 phenotypes at age 6m and 6 at ages 18m and 30m. At each age, 3 phenotypes, each comprising 20-30% of children, were identified, one with episodes triggered mainly by infections and cold weather and one with “other” triggers predominating. Other phenotypes were characterised by moderate or mild symptoms and differed in patterns of triggers. Phenotypes were similar at different ages. Among children with mild wheeze, >60% were classified longitudinally as “transient early” or “prolonged early wheezers” while >34%, >46% and >63% of children in the severe groups at ages 6m, 18m, and 30m respectively were classified as “persistent wheezers”.

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Funding: European Respiratory Society/Marie Curie Joint Research Fellowship - Number MC 1614-2010.

P1500
First and second trimester fetal size and asthma outcomes at age ten years

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Introduction: Childhood asthma is a common condition characterised by relapse and remission. Here we sought to identify the precision of physiological measurements made in 5-year-olds for predicting asthma outcome at 10 years of age.

Methods: As part of a cohort study, 5 year old children attended a clinical assessment which included skin prick reactivity, spirometry and bronchodilator response. A respiratory symptom questionnaire was completed at ages 5 and 10 years. Children were categorised as having persistent asthma, early remittent asthma, later onset asthma or being non-asthmatic.

Results: Of the 1924 originally recruited, questionnaire data were available in 808 children at both 5 and 10 years of age including 37 with persistent asthma, 30 with early remittent asthma and 33 with later onset asthma. Skin prick reactivity was determined in 483 5-year-olds, spirometry in 410, bronchodilator response (BDR) in 164 and FENO in 110. Asthma had sensitivity of 82% [95% CI 68, 92] and specificity of 57% [95% CI 42, 68] for predicting persistent asthma in symptomatic 5-year-olds and a sensitivity of 72% [95% CI 50, 87] and specificity of 79% [95% CI 78-80] for predicting later onset asthma in asymptomatic 5-year-olds. Regardless of asthma status at 5 years, FENO >10.7ppb had a sensitivity of 62% and a specificity of 89% for asthma at 10 years. Spirometry and BDR were not predictive of later asthma outcomes.

Conclusions: In this community-based cohort, objective physiological measurements taken in 5-year-olds were able to predict asthma outcome in later childhood. The absence of atopy or elevated FENO in a young child with asthma or asthma-like symptoms may be helpful in predicting low risk for future asthma symptoms.

P1501
Fetal and infant growth is associated with wheezing in preschool children.

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Background: Birth size is associated with wheezing in childhood. Not much is
known about the role of longitudinal growth in fetal life and infancy on asthma symptoms. Our aim was to examine the associations of fetal and infant growth characteristics with wheezing in preschool children.

Methods: This study was embedded in a population-based prospective cohort study among 5,125 children. Information on second and third trimester fetal growth (fetal weight, head circumference, abdominal circumference, fetal estimated weight) was obtained by multiple ultrasounds during pregnancy. Infant growth (length, weight) was repeatedly measured at the Community Health Centres at the ages of 3, 6, and 12 months. All growth characteristics were converted into age and sex adjusted standard deviation scores (SDS). Parental report of wheezing until the age of 4 years was yearly obtained by questionnaires.

Results: Fetal growth characteristics were not associated with wheezing at all ages. Infant weight gain was associated with the risk of wheezing in the first 2 years (Odds ratios (OR) age 1 year: 1.23 (95% Confidence Intervals (CI): 1.02, 1.48); age 2 years: 1.42 (95% CI: 1.22, 1.66)) per SDS weight gain in the first 3 months of life. These effect estimates were higher for children who were fetal growth restricted from the 2nd trimester to birth (at age 1 year: 1.32 (1.10, 1.57), age 2 years: 1.26 (1.04, 1.54)).

Conclusions: Increased weight gain during the first 3 months after birth is associated with increased risk of wheezing in the first 2 years of life, especially after fetal growth restriction. Our results suggest that abnormal fetal and infant growth might influence the development of asthma in childhood.

P1502
Longitudinal development of lung function in extremely preterm infants

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Introduction: With the advent of modern neonatal intensive care, survival after extreme preterm (EP) birth increased considerably. Large cohorts of subjects born EP are now approaching adulthood; their lifelong pulmonary prospects being basically unknown.

Aims: To construct spirometric growth curves to early adulthood for subjects born EP.

Methods: Two area-based birth-cohorts of subjects born in 1982-85 and 1991-92 at gestational age <28 weeks or with birth weight <1000 grams (n=81) and individually matched control subjects born at term (n=74) were examined in 2001 and 2009. Paired multiple linear regression models were constructed to assess growth patterns.

Results: Most measures of lung function were significantly reduced in subjects born EP over the full study period. Mean growth of FEV1 through puberty was 1.5 liters in both preterm and control subjects, and there was a small but not significant growth from age 18 to 25.

*Mean values (95% CI).

Conclusions: Lung function deficits after EP birth persists to adult life. Growth in lung function was parallel in subjects bornEP and at term, and no signs of age related decline was observed at age 25.

P1503
Factors for lower respiratory illnesses (LRI) in infants < 32 wks gestational age (GA): Do they differ by type of illness?

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Introduction: Factors present in infancy have been associated with respiratory outcomes in childhood. Risk factors for wheeze in adults differ from those in children, for example female gender and active smoking. Here we test the hypothesis that physiological outcomes measured in infancy are associated with persistent respiratory outcomes in eighteen year olds.

Methods: As part of a longitudinal birth cohort study, measurements of infant lung function and atopy were made in infancy. Participants were followed up with at ages 6, 12 and 18 years. Based on reported symptoms, individuals were categorised as remittent wheeze, later onset wheeze, persistent wheeze and no wheeze.

Results: Of the 253 individuals originally recruited, 148 were followed up at age 18 years including 13 with persistent wheeze, 13 with remittent wheeze, 23 with later onset wheeze and 99 with no wheeze. Compared to the no wheeze group, persistent wheeze was independently associated with reduced lung function at one month (mean reduction% predicted V’maxFRC 43 [95% CI 13, 74]), increased length at one month (40% increase risk per cm increase [95%CI 6, 187]), atopy in infancy (OR 5.2 [95%CI 1.1, 23.8]) and current smoking (OR 6.1 [95%CI 1.3, 30.7]). Later onset wheeze was associated with female sex (OR 4.0 [95% CI 1.5, 11.4]). Remittent wheeze was not associated with the risk factors considered in the analysis.

Conclusion: Although female sex and active smoking are risk factors for wheeze in adulthood, the presence of reduced lung function and atopy in infancy remain risk factors for ongoing respiratory symptoms in young adults.

P1504
Preterm birth and inhaled corticosteroid usage in 6-19-year-olds – A Swedish national cohort study

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Objective: To construct spirometric growth curves to early adulthood for subjects born EP.

Methods: Area-based birth-cohorts of subjects born between 1982 and 1992 in 2 Italian regions (ACTION study) and those born in weeks 24-28 were used to construct growth patterns.

Results: Degree of immaturity, expressed as completed gestational weeks at birth, had an inverse dose-response relationship with ICS usage. Compared to children born between 31 and 37 weeks gestation, the odds ratio for ICS usage increased with the degree of prematurity, from 1.10 (1.08-1.13) for children born in weeks 37-38, to 2.28 (1.96-2.64) for children born in weeks 24-28, after adjustment for socio-economic confounders and perinatal mediators.

The increase in ICS usage with decreasing gestational age at delivery was similar in boys and girls and declined with older age.

Conclusion: Preterm birth increases the risk of ICS usage in 6-19 year olds by degree of immaturity, all the way from extremely preterm to early term birth.

P1505
Early life antecedents of persistent wheeze in young adults

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Conclusion: Although female sex and active smoking are risk factors for wheeze in adulthood, the presence of reduced lung function and atopy in infancy remain risk factors for ongoing respiratory symptoms in young adults.

asthma/atopy, obstetrical and perinatal variables, breastfeeding and current envi-
ronmental factors (siblings, smoking/dampness at home, traffic) were assessed as possible predictors through multivariable regression analysis.

1009/1413 children had assessment-interview. Bronchitis/asthmatic bronchitis (18.8% of children) were significantly associated with lower GA, parental asthma (Odds ratio.OR 1.80) and day care (OR 2.00), while female sex and foreign mother were protective (OR 0.71 and 0.56). Risk of bronchitis/pneumonia (16.2%) was significantly reduced at higher GA, in twins (OR 0.45), and in infants discharged from NICU in april-september (OR 0.63). 14% of children were admitted to hospital for LRI; they were significantly more likely to have been exposed to maternal smoking in pregnancy (OR 1.67), have had birthweight <10° centile (OR 2.0) and BPD (OR 2.1); infants with LRI requiring O2 or ventilation (5.2%) had the same risk factors.

Wheezing and LRI admissions had different risk profiles: the former were similar to those in general populations studies, while the latter were associated with prenatal factors influencing lung growth (intrauterine growth restriction, smoke) and BPD.
Factors associated to an earlier wheezing episode during the first year of life in Europe and Latin America: The EISL study

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Background: There is scarce information about what factors might influence the time to the first wheezing episode in infants.

Methods: The “Estudio Internacional de Sibilancias en Lactantes (EISL)” included 13,684 infants who wheezed at least once in the first year of life, recruited from 15 centers in 6 Latin American countries (n=12,045) and from 5 centers in 2 European countries (n=1,639). A multivariate Cox regression analysis was performed using as dependent variable the time to the first wheezing episode. The regression included the following factors: gender, parental asthma or rhinitis, infant exposure to second-hand smoking in pregnancy, colds (a wheeze in the first 3 mo), nursery school, breast feeding >= 3 mo, number of siblings, persons at home, mould stains on walls, university studies of mother, Afro-American ethnicity, and pets at home. An adjusted hazard ratio (aHR) of the pooled whole population and also separately for EU and LA was calculated.

Results: Adjusted hazard ratios (aHR) for an earlier episode of wheezing in the first year of life

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
<th>Europe</th>
<th>Latin America</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
</tr>
<tr>
<td>Cold(s) during the 1st 3 months</td>
<td>1.84 (1.77-1.91)</td>
<td>1.85 (1.66-2.06)</td>
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<td>Breast feeding &gt; 3 months</td>
<td>0.93 (0.90-0.97)</td>
<td>0.98 (0.88-1.09)</td>
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<tr>
<td>Mould stains on household walls</td>
<td>1.04 (1.00-1.08)</td>
<td>1.12 (0.95-1.33)</td>
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<tr>
<td>University studies in mother</td>
<td>0.99 (0.96-1.03)</td>
<td>0.82 (0.71-0.95)</td>
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<tr>
<td>Infant eczema</td>
<td>1.02 (0.98-1.05)</td>
<td>1.25 (1.10-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Some factors usually shown to be a risk factor for wheezing are not associated to a shorter period of time to the first episode. Furthermore, some delaying or advancing factors are different in Europe as compared to Latin America.

Long-term evolution of virus-induced and multi-trigger wheeze in children of the EGEA study

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Background: Recent guidelines have proposed different phenotypes according to triggers (episodic/virus (EV) and multi trigger wheeze (MTW)) in preschool children. Studies aimed at characterizing asthma evolution according to these phenotypes are seldom.

Aims: To investigate lung function and asthma evolution up to adulthood between MTW and EVW in childhood.

Methods: 588 children, aged 10.9±3.0 years included in EGEA study were classified as non wheezer (n=265), EVW (wheeze only with viral infections and asymptomatic between episodes, n=131) and MTW (wheeze with viral infections and between episodes with triggers such as dust, tobacco smoke, exercise, and cold exposure in affecting the development of asthma in urban and rural settings.

To determine the relationship of indoor endotoxin and manifestations of respiratory symptoms in urban children in Hong Kong.

Methods: Random sample of schools for children aged 7 to 11 years were recruited through the school system. Parents completed the locally validated ISAAC questionsnaires with additional questions about the home environment. Random subgroup of subjects was recruited for SPTs and dust samples were collected according to the ISAAC Phase II protocol. Endotoxin levels were log-transformed before analysis.

Results: 3,546 primary schoolchildren were screened with a participation rate of 96%. A random subsample of 1,303 subjects has been skin-tested with 439 also provided mattress dust samples. Among them, 37 (8.4%) had at least one wheezing attack in the past year and 47 (10.7%) had a physician diagnose of asthma. The median (interquartile range) of endotoxin concentration (EU/m³) and log (EU/m³) were 12.9 (6.25) and 547 (230-1,137) in those without current wheeze; they were 34 (19-83) and 1,689 (853-3,301) in those with current wheeze. The differences were significantly different (p<0.01) adjusted for confounders.

Among those with a asthma diagnosis, higher endotoxin level was associated with use of asthma medication in the past year.

Conclusion: Higher level of endotoxin level in this urban sample of schoolchildren is associated with wheezing and increased use of asthma medication among known asthmatics. Further studies are needed to reveal the possible roles of microbial exposure in affecting the development of asthma in urban and rural settings.

Does maternal smoking play a role as an inducer, rather than trigger, of asthma and respiratory symptoms?

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Background: Asthma is a complex chronic disease arising from the interaction of genetic and environmental factors. In children, it is difficult to separate any role of maternal smoking in the antenatal induction of asthma from a later role as a symptom trigger, as most mothers who smoke in pregnancy continue to smoke after their child’s birth.

Aim: To estimate the association between parental smoking and asthma and respiratory symptoms in adults, and to compare findings with those for current exposure to environmental tobacco smoke (ETS).

Methods: The Midspean Family Study included offspring aged 30-59 years, whose parents reported their smoking habits as part of an epidemiological study 20 years earlier. Offspring completed a questionnaire and underwent spirometry. We used
P1513\textbf{Clinical evaluation of RV wall stress in pulmonary arterial hypertension: A follow-up study using magnetic resonance imaging}\n
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Background: In pulmonary arterial hypertension (PAH) survival is strongly associated with right ventricular (RV) function and its ability to adapt to the increased pulmonary artery pressure (PAP). RV remodeling to the increased load is often characterized by dilatation, and hypertrophy. RV wall stress is a simple parameter that contains the effects of PAP, dilatation and hypertrophy. Therefore this study aims to evaluate RV wall stress in patients during follow-up.

\textbf{Methods and results:} At baseline 53 patients underwent magnetic resonance imaging (MRI) and right heart catheterization (RHC). In all patients RV end-systolic wall stress (RVESWS) was calculated using the law of Laplace. Eight patients died during the first year of follow-up and therefore 45 patients underwent MRI and RHC after 1-year follow-up. During a median 1-year term follow-up of 57 months another 10 patients died. At baseline, RVESWS appeared to be similar in survivors and non-survivors (n=53, p=0.765). In contrast, change of RVESWS during the 1-year period was significantly (p=0.014) between survivors and non-survivors. Survivors showed a decrease in RVESWS during 1-year follow-up, whereas non-survivors showed an increase of RVESWS during 1-year follow-up.

Kaplan-Meier analysis showed a higher mortality rate in patients with an increase of RVESWS >17 mmHg than in patients with an increase of RVESWS ≤17 mmHg or a decrease of RVESWS during follow-up (n=48, p<0.001).

Conclusion: Progressive RV failure is characterized by an increase of RVESWS.

P1514\textbf{Ventilation perfusion lung scan in pulmonary veno-occlusive disease}\n
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Introduction: Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary arterial hypertension (PAH) that remains poorly understood and is both difficult to diagnose and treat. Histological proof is required for a definitive diagnosis of PVOD; however, this approach is hazardous in patients with pulmonary hypertension and therefore surgical lung biopsy is not recommended. In recent joint ERS/ESC guidelines, ventilation and perfusion (V/Q) lung scan was recommended to look for chronic thromboembolic pulmonary hypertension and it has been suggested that unmatched perfusion defects may suggest PVOD.

![Figure 1. Comparative evaluation of the V/Q scans between iAP and PDVQ groups.](image-url)
Aim of the study: To evaluate the interest of V/Q lung scan in the non-invasive approach to screen PVOD patients.

Methods: V/Q lung scans from 70 patients with idiopathic PAH and 56 patients with confirmed or highly probable PVOD, were reviewed in double blind.

Results: The vast majority of V/Q lung scan were normal or with no significant abnormalities in both group of patients. No differences in ventilation or perfusion lung scans were observed between idiopathic and PVOD patients (p > 0.05). No differences were observed between confirmed (n=31) or highly probable PVOD (n=25). Unmatched perfusion defects were found in 7 (10%) idiopathic PAH patients and 4 (7.14%) PVOD patients (p > 0.05).

Conclusion: Unmatched perfusion defects were rarely observed in idiopathic PAH or PVOD and V/Q lung scan may be not useful to discriminate PVOD.

P1515
Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension
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Background: Accurate measurement of left ventricular filling pressure (LVEDP) is important to distinguish between Group 1 pulmonary arterial hypertension (PAH) and Group 2 pulmonary hypertension from diastolic heart failure (PH-HFpEF).

Methods: We prospectively performed catheter catherization on 62 patients referred for evaluation of PH and compared the LVEDP at end-expiration to: a) the pulmonary capillary wedge pressure manually determined at end-expiration (PCWP-EXP) and b) the PCWP determined electronically (PCWP-digital).

Results: The PCWP-EXP was a more reliable measure of the LVEDP (mean 13mmHg vs 12.4mmHg, p=NS) than the PCWP-digital (mean 8mmHg vs 12.4mmHg, p=0.05). Bland-Altman analysis of PCWP-digital and LVEDP revealed a mean bias of -4.4 mmHg (95% limits of agreement -11.3mmHg to 2.4mmHg). Bland-Altman analysis of PCWP-EXP and LVEDP revealed a mean bias of 0.7mmHg (95% limits of agreement -5.5mmHg to 7.9mmHg). If the PCWP-digital were used to define the LVEDP, 11 patients (18%) would have been misclassified as having PAH rather than PH-HFpEF. Interestingly, 8 of these 11 patients either mortfuid obesity or hypoxia. In contrast, no patients were misclassified as PAH instead of PH-HFpEF using the PCWP-EXP to define LVEDP.

Conclusions: The common practice of using PCWP-digital measurements instead of PCWP-EXP measurements results in significant underestimation of the LVEDP. In our study, this translated to almost 20% of patients being misclassified as having PAH rather than PH-HFpEF. Thus, reliance on PCWP-digital measurements should be avoided as this may lead to the inappropriate use of pulmonary vasodilators.

P1516
Increased renin-angiotensin-aldosterone system activity in lungs of patients with idiopathic pulmonary arterial hypertension
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Studies have reported over-activation of the sympathetic nerve system (SNS) in patients with idiopathic Pulmonary Arterial Hypertension (iPAH). Since the Renin-Angiotensin Aldosterone System (RAAS) is closely related to SNS and the lungs are the major site for angiotensin 2 formation, we hypothesized that RAAS-activity is increased in iPAH.

Pulmonary endothelial cell (P-EC) cultures were generated from lung specimens of iPAH-patients and 4 (7.14%) PVOD patients (p > 0.05). P-EC of iPAH-patients produced significantly more angiotensin 2 upon angiotensin 1 incubation, compared to control. Interestingly, enalapril normalized angiotensin 2 production (Fig. 1B). In addition, pulmonary arteries of iPAH-patients exhibited increased AT1R expression and accentuated SRC-activity (Fig. 1C,D).

Conclusions: This study demonstrates increased RAAS-activity in lungs of iPAH-patients, illustrated by elevated ACE-activity and AT1R signalling. Future studies will focus on the effects of chronic inhibition of RAAS on pulmonary vascular remodelling in iPAH.

P1517
Changes in right ventricular mass are unrelated to changes in pulmonary pressures in pulmonary arterial hypertension
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Background: In pulmonary arterial hypertension (PAH), chronic pressure overload leads to right ventricular (RV) dilatation, hypertrophy and ultimately RV failure and death. Yet, the relevance of changes in RV mass and the interaction with changes in pulmonary pressure have never been investigated.

Objectives: To assess the relationship between changes in pulmonary pressure, volumes in RV mass and survival in PAH patients under PH-HFpEF targeted therapies.

Methods: 45 patients underwent right heart catheterization to measure mean pulmonary artery pressure (mPAP) and cardiac magnetic resonance to assess RV mass before and after 12 months of therapy. RV mass was indexed for body surface area. During long-term follow-up, 11 patients died.

Results: At baseline, survivors and non-survivors showed a similar mPAP (p=0.43) and RV mass index (p=0.06). RV mass index correlated to mPAP (R=0.51, p<0.01). At one-year follow-up, survivors (8 out of 12) showed an unchanged RV mass (-8±28%) and non-survivors (3 out of 3) (p=0.86). Overall, RV mass increased by 11±26% (p=0.03). Survivors showed an increased RV mass (17±25%; p<0.01). non-survivors showed an unchanged RV mass (-7±11%; p=NS). Changes in RV mass were unrelated to age (p=0.50) or gender (p=0.44). Changes in RV mass were unrelated to changes in mPAP (R=0.14; p=0.37).

A decreased RV mass was associated with mortality (HR: 0.95; 95%-CI 0.91-0.99; p=0.02) whereas changes in mPAP did not relate to mortality (HR: 1.01; 95%-CI 0.98-1.02; p=0.25).

Conclusions: In PAH, changes in mPAP were not followed by changes in RV mass. An increased RV mass during follow-up was associated with a favorable prognosis.

P1518
Systemic hypoxia contributes to pulmonary hypertension in heart failure
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Background: The classical mechanism for pulmonary hypertension (PH) in heart failure (HF) is related to vasoconstriction in pulmonary veins pressure surges leading to an increase in LV filling pressure. However, much of the PH in HF is reversed by ventilation. This suggests a reactive component to the elevated pulmonary vascular resistance (PVR) that is likely related to dysregulation of vascular smooth muscle tone. Although the cause of this dysregulation is unclear, hypoxia may play a role. We examined whether variations in resting systemic O2 levels influence PVR in HF.

Methods: Thirty-nine patients (54±9 yr, LVEF 20±6%, NYHA class I-III) undergoing right heart catheterization for pre transplant assessment were studied. PVR was derived from pulmonary arterial and wedge pressures measured via Swan Ganz catheter and cardiac output measured via direct Fick. Mixed venous and arterial blood was drawn from the pulmonary and radial arteries for measurement of PaO2, PaCO2, SaO2, SvO2 and endothelin-1 (ET-1).

Results: Group mean PVR, PaO2, PaCO2, SaO2 and SvO2 were 303±215 dyne/s/cm2, 72±12 mmHg, 32±4 mmHg, 94±4% and 57±11%, respectively. PVR was negatively correlated with PaO2, PaCO2, SaO2 and SvO2 (r=-0.53, -0.62, -0.48, -0.67, respectively, all P<0.01). Multiple linear regression suggested that SvO2 was the strongest predictor of PVR. In combination, PaCO2, PaO2, SaO2 and SvO2 accounted for ~60% of the variance in PVR. In addition, ET-1 was related to both SvO2 (r=-0.75) and PVR (r=0.50) (P<0.1).

Conclusion: Systemic hypoxia, particularly a low SvO2, appears to play a role in PH and elevated PVR in HF. We suggest a hypoxia-mediated increase in the release of the vasoconstrictor ET-1 as a likely mechanism. NIH HL71478
SR was not associated with prognosis \((p = 0.9)\). Survival was worse in patients diagnosed \((n = 6)\) or during follow-up \((n = 43)\).

Venous oxygen saturations were lower in patients developing flutter (58\% vs. 61\%) but initial mixed arrhythmia. Baseline age, exercise capacity and pulmonary haemodynamics were not significantly different between the flutter and AF group but initial mixed venous oxygen saturations were lower in patients developing flutter (58\% vs 64\%, \(p = 0.02\)). Management including chemical or DC cardioversion and/or ablation therapy maintained 59% of patients in sinus rhythm (SR). Failure to maintain SR was not associated with prognosis \((p = 0.9)\). Survival was worse in patients developing flutter rather than AF (figure).

**Conclusions:** Atrial arrhythmias are common in PH. AF is more commonly associated with PH-LHD and developing flutter was associated with poorer survival. Further analysis of optimal management strategies is required.

**Methods:** A six-year retrospective analysis was conducted of \(>1000\) newly diagnosed patients with PH.

**Results:** There were 264 pre-existing cases of atrial fibrillation (AF) including 29\% pulmonary arterial hypertension (PAH), 53\% PH due to left heart disease (PH-LHD), and 7\% chronic thromboembolic PH (CTEPH). PAH and CTEPH were more common (45\% and 24\%) than PH-LHD (17\%) as the underlying cause of PH in the 29 patients who had atrial flutter (flutter) diagnosed prior to PH diagnosis \((p < 0.05)\). 49 new diagnoses of flutter or AF were made at PH diagnosis \((n = 6)\) or during follow-up \((n = 43)\). ~7\% of all PAH patients developed an atrial arrhythmia. Baseline age, exercise capacity and pulmonary haemodynamics were not significantly different between the flutter and AF group but initial mixed venous oxygen saturations were lower in patients developing flutter (58\% vs 64\%, \(p = 0.02\)). Management including chemical or DC cardioversion and/or ablation therapy maintained 59% of patients in sinus rhythm (SR). Failure to maintain SR was not associated with prognosis \((p = 0.9)\). Survival was worse in patients developing flutter rather than AF (figure).
to human PAH and examined their possible role as predictors of activity and progression of disease.

18 patients with idiopathic and familial PAH and 20 healthy control subjects were studied. Circulating fibrocytes, identified as CD11b+CD34+vimentin+ cells and membrane CD11b expression were quantified by flow cytometry. The in vitro differentiation capacity of PBMC to fibrocytes was quantified. We observed a slight decrease in the percentage but not in the number of circulating fibrocytes in the blood of PAH patients, compared with healthy control subjects (0.67±0.15% in control subjects vs 0.22±0.04% in PAH patients, p<0.05). Accordingly, a significant decrease in the percentage of differentiated CD45+vimentin+ cells in PBMC culture from PAH patients was observed (73.4±3% in control group vs 61.2±2% in PAH patients, p<0.05). Interestingly, the mean fluorescence intensity of CD11b was significantly increased on circulating fibrocytes in PAH patients (111±16 in control group vs 216±7±247 in PAH patients, p<0.0001), indicating their increased activation state.

Our data suggest that a more detailed analysis of circulating fibrocyte function and activation is needed in PAH patients.

P1524 Role of mast cells and chymase in pulmonary vascular remodeling

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Rationale: Mast cells (MCs) are implicated in chronic inflammation and tissue remodeling. However, a systematic investigation of pulmonary MCs/MC chymase is yet missing in idiopathic pulmonary arterial hypertension (IPAH) and chronic obstructive pulmonary disease (COPD).

Methods: Lung tissues obtained from donors, and IPAH and COPD patients undergoing lung transplantation were formalin-fixed and paraffin-embedded, followed by blue staining (TB) for staining MCs and immuno staining for MC chymase. Total and perivascular MCs were determined by counting MCs under light microscope equipped with computerized morphometric system. Perivascular MCs were categorized as granulated and degranulated and an index of granulation (IOG) (number of granulated/degranulated MCs) was determined.

Results: Pulmonary MCs were prevalent in IPAH and COPD patients; furthermore, perivascular MC count was significantly increased in the resistance vessels of patients (p<0.05 vs donors). Notably, the IOG was decreased by about 8 and 5 folds in IPAH and COPD patients, respectively (vs donors). Chymase-positive MCs were increased by 16 and 10 folds in IPAH and COPD patients, respectively (vs donors). The perivascular chymase-positive MCs were significantly increased in IPAH and COPD patients (p<0.05 vs donors). Interestingly, the chymase-positive MC subpopulations were about 42% and 48% of the MCs in IPAH and COPD patients, respectively; whereas it was 10% in donors.

Conclusion: The chymase released from activated perivascular MCs may potentially contribute to the pulmonary vascular remodeling in IPAH and COPD. Future studies are essential to substantiate the findings and to elucidate underlying pathomechanisms.

P1525 Frequency and impact on prognosis of signs of pulmonary veno-occlusive disease on high resolution computed tomography in patients with scleroderma associated pulmonary arterial hypertension

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Introduction: Pulmonary veno-occlusive disease (PVOD) is an uncommon form of pulmonary arterial hypertension (PAH) characterised by a progressive obstruction of small pulmonary veins. PVOD has been frequently reported in patients with scleroderma related PAH (SSc-P AH). High resolution chest computed tomography (HRCT) is a non-invasive diagnostic tool used to screen for PVOD. However, no data are available in SSc-P AH patients.

Aims: To evaluate the frequency and the impact on prognosis of signs of PVOD on HRCT in SSc-P AH.

Methods: We reviewed HRCT data in 34 consecutive SSc-P AH patients and 30 systemic sclerosis (SSc) patients.

Results: Lymph nodes enlargement (57.7% vs 3.6%), centrilobular ground-glass opacities (46.2% vs 10.7%) and septal lines (73.1% vs 7.1%) were significantly more frequent in SSc-P AH patients as compared to SSc patients (all p<0.05). Interestingly, the mean and pulmonary artery enlargement were significantly more frequently observed in SSc-P AH patients (p<0.001). Pleural effusion was observed in one patient (3.8%) in the group SSc-P AH, whereas no SSc patient had a pleural effusion.

In SSc-P AH patients with ≥2 radiological signs of PVOD was significant lower compared to those ≤1 radiological sign of PVOD (P<0.05).

Conclusion: Signs of PVOD are frequent on HRCT in patients with SSc-P AH compared to SSc patients without PVOD. These signs allow clinicians to detect PVOD in SSc-P AH patients. Survival in affected patients is poor.

P1526 How does variation of the bag volume in inert gas rebreathing cardiac output measurements influence the reproducibility in patients with pulmonary diseases?

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Background: Cardiac output (CO) is an important hemodynamic parameter, however its determination is difficult in daily clinical routine. Non-invasive inert gas rebreathing (IGR) showed promising results in recent investigations with the volume of the rebreathing bag (Vb) being an important factor. The aim of our study therefore was to evaluate the influence of different Vb on the reproducibility of IGR.

Methods: The collective consisted of 45 patients (age 26 to 88 years). The CO was determined in patients with obstruction (group A), restriction (group B) and pulmonary healthy controls (group C). For Vb of 2200 ml, 1700 ml and 1200 ml two repeated measurements were taken each. The determination of lung function was performed using bodyplethysmography.

Results: Pulmonary obstruction was diagnosed in 12 patients (PEV, 52±21%) and restriction in 11 patients (VC 61±16%). The mean CO did neither differ between the groups (p>0.1) nor for the different Vb (p>0.2). The mean bias between the repeated measurements was 0.2±0.99ml/m² for Vb=2200ml, 0.4±0.79ml/m² for Vb=1700ml and 0.3±0.79ml/m² for Vb=1200ml. There was no statistically significant difference between the groups for the different Vb=2200ml (p=0.7), 1700ml (p=0.4) and 1200ml (p=0.2).

Conclusion: The reproducibility of IGR is not negatively affected by Vb, so it can be varied between 2200 and 2200 ml. This is especially important when Vb has to be reduced due to incomplete inspiration. The trend to a worse reproducibility of measurements at rest should be further investigated. For now, measurements should only be compared directly when identical Vb were used.

P1527 Characteristics of patients with pulmonary arterial hypertension associated with congenital heart disease in the French PAH registry

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Background: Epidemiological data relative to pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) are scarce. In the first French PAH registry conducted in 2002-2003, CHD accounted for 11.3%.

Objective: To analyze PAH associated with CHD in patients enrolled in the second prospective PAH registry initiated in 2006.

Methods: PAH-related clinical and outcome data were reviewed and analyzed from the registry.

Patients and results: 2585 patients with PAH were enrolled in 26 PAH centers. CHD-PAH (n = 255) accounted for 9.8%, including 95 isolated pre-tricuspid shunts (mainly ASD), 134 isolated post-tricuspid shunts (mainly VSD), 11 combined pre-and post-tricuspid shunts and 15 complex CHD. 60% of patients were females and mean age at diagnosis was 37 years. The diagnosis of PAH was done simultaneously with the diagnosis of CHD in 37% of the cases and in 60% PAH appeared during the follow-up of CHD. At study entry, 52% of patients were in NYHA functional class (FC) III or IV, 6MWD was 370±105 m and pulmonary hemodynamics were: mPAP= 59±60 mmHg, CI= 2.7±1.1 L/min/m² and PVRs= 12.5±3.3 WU. 47% of NYHA II and 43% of NYHA III patients were not receiving PAH-specific therapies. In treated patients (n = 164), NYHA FC improved (59% in NYHA FC II at last follow-up). During the 3-year follow-up period, 20 patients died and 7 patients were transplanted.

Conclusions: PAH is a complication of a previously known CHD in 60% of cases. ASD is the main CHD that is diagnosed concomitantly or after PAH. Less than a half of NYHA III patients are offered PAH-specific therapies. Mortality was low during the short period of follow-up.
Among the 350 patients who met the inclusion criteria, 100 (28.5%) were younger patients despite a less severe haemodynamic impairment. Patients with IPAH and ArPAH. Patients >70 yr have a worse outcome than 18–70 yr. Clinical and haemodynamic characteristics at time of diagnosis are shown in the Table. Survival rates at 1, 2 and 3 years were 79%, 60% and 47% in those >70 yr, as compared to 92%, 84% and 76% in the 18-70 yr group, respectively (p<0.001).

Conclusions: These results show an increasing proportion of elderly male among patients with IPAH and ArPAH. Patients >70 yr have a worse outcome than younger patients despite a less severe haemodynamic impairment.

P1529  
Assessment of operability by means of CTPA and perfusion SPECT in patients with chronic thromboembolic pulmonary hypertension  
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Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) is curable with pulmonary endarterectomy (PEA). The criteria for identification of PEA-amenable patients need to be standardized. The aim of this study was to evaluate the value of rigidly registered CT pulmonary angiography (CTPA) and perfusion SPECT in differentiating between operable and non-operable patients.

Methods: 49 patients with CTEPH (21 men, 58±13 years) were evaluated for PEA by interdisciplinary board using available diagnostic information and served as the gold standard.SPECT was evaluated by a lobe based visually assessed perfusion score ranging from 0 [no perfusion] to 1 [normal perfusion],after which the percentage of vascular obstruction (PVO) was calculated: PVO = [1 – Perfusion score] × 100. By CTPA, the vascular obstruction index (OI) of central, peripheral vessels reaction to different stimuli may be a sign of peripheral vasomotor reaction during local airway cooling. Methods: The reaction of peripheral vessels of finger (digitales palmares proprius) during and after 3-min isocapnic cold (-20°C) air hyperventilation was studied in 11 healthy persons and 31 patients with chronic pulmonary diseases (bronchial asthma and chronic bronchitis) having CARR. The amplitude of pulse wave (AWP) was evaluated by photoplethysmography of finger. Results: A phase reaction of finger artery to cold air inhalation was revealed in healthy persons. By the end of the 3rd min of hyperventilation there was a progressive drop of AWP (30±2.8±7.6%) as a result of vasconstriction with further short-term vasodilation proved by the growth of AWP higher than the initial level (8.7±5.9±6.5%) immediately after provocation cessation and its additional fall on the 5th min of recovery (-15.5±7.3%), which meant a repeated vessel spasms. In group of patients cold air inhalation led to sustained AWP drop both during provocation (-21.4±8.9%) and recovery period (1st and 5th min) -26.2±11.0% and 15±15.6% respectively. There was a correlation among airway reaction, changes in peripheral blood flow, skin temperature at the beginning and at the end of the bronchoprovocation in patients. 

Conclusions: Revealed abnormalities in peripheral microcirculation in patients with the changed airway responsiveness can be an early sign of systemic vascular dysfunction.

P1530  
Metabolic and cardiopulmonary responses to the incremental shuttle walk test vs. six-minute walk test in healthy older adults  
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Whether the incremental shuttle walk test (ISWT) induces a higher physiological stress compared to six-minute walk test (6MWTT) in patients remains controversial. However, previous studies did not include healthy subjects. We compared physiological responses to the ISWT and 6MWTT in healthy adults (38 men, aged 60±5.10). Secondly, peak oxygen uptake (VO2peak) in these tests were compared to predict values of a maximal cycle-ergometer test. In a randomized order and alternate days, 80 participants completed three 6MWTTs and three ISWTs. VO2, CO2 output (VCO2), minute ventilation (VE), and heart rate (HR) were monitored by a portable telemetric system during each test. Physiological responses were linear during ISWT and exponential during 6MWTT. We could calculate deficit-0.2 (1072±622 mL) and VO2 time constant–tau+0.2 (56±19 s) in all participants by exponential fittings (R2=0.90±0.005). During the 6MWTT, VO2peak (1672±441 mL/min), VCO2 (1443±439 mL/min), VE (46±16 L/min) and HR (129±24 bpm) were not significantly different compared to ISWT (respectively 1714±544 mL/min; 1591±582 mL/min; 51±19 L/min; and 132±2 bpm). The distance covered correlated with peak VO2 for ISWT (r=0.738; p=0.001) and 6MWTT (r=0.652; p=0.001) with no difference between correlation coefficients (p=0.234). Estimated peak VO2 (1541±422 mL/min) was not significantly different from measured peak VO2 obtained during ISWT and 6MWTT being considered to be closer to a maximal exercise test than 6MWTT. ISWT does not induce a greater physiological responses in healthy adults. Larger studies should be performed in patients for better physiological comparisons between these walking tests.

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Evaluation of heliox or oxygen breathing on improved quadriceps muscle oxygen delivery during exercise in COPD

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Introduction: It is known that both normoxic heliox and pure oxygen breathing significantly increase locomotor muscle O2 availability during exercise. However, it remains unknown which of the two gases is the most beneficial in terms of enhancing exercise tolerance and locomotor muscle O2 availability.

Methods: 12 COPD patients [FEV1=42±9% of predicted] performed 3 constant-load exercise tests at 75% of maximum work rate while breathing air, normoxic heliox (He: 32±6% vs O2: 68±4% at rest), and ID (using indocyanine green) over the last minute of exercise.

Results: CO by PF exceeded that by ID by 2.6±0.3 L/min (Mean±SE) averaged across all exercise levels (p=0.001).

Conclusion: Compared to ID, PF overestimates CO across different levels of exercise but its slope of change relative to VO2 is very similar. Hence PF can accurately estimate changes from resting CO during exercise in COPD.

P1534 Dynamic pathophysiology in stable COPD patients with severely reduced exercise capacity
Ryoo Mukura, Toru Hiraga, Keisuke Miki, Seigo Kitada, Kenji Yoshimura, Yoshitaka Tateishi. Respiratory Medicine, National Hospital Organization Toneyama Hospital, Toyonaka, Osaka, Japan

Introduction: The survival prognosis of COPD patients with severely reduced exercise capacity is extremely poor. However, the dynamic pathophysiology of these patients, including sympathetic activation and lactic acidosis, remains to be accurately established. Thus, we performed this study to clarify the differences in the dynamic pathophysiology of four COPD patient groups classified according to their exercise capacity.

Methods: Ninety-one COPD patients (82 males, 9 females; average age, 69.7±6.8 years) underwent incremental CPET using a cycle ergometer. During CPET, we measured the patient levels of arterial blood gases, lactate, and catecholamines.

Results: We found that the pathophysiology of the COPD patients was different among the groups. Patients with severely reduced exercise capacity (peak oxygen uptake < 654 ml/min) were characterized by the following: (i) exercise-induced rapid decrease of arterial oxygen pressure (PaO2-slope: -7.8±0.7 mmHg/100 ml); (ii) sympathetic activation at low-grade workload (plasma norepinephrine level, 1.4±0.94 ng/ml at 20 W); (iii) little change in lactic acidosis; (iv) a limitation in the increase of ventilation; and (v) impaired gas exchange. The norepinephrine increase exhibited during exercise was significantly correlated (r = 0.94±0.08) with the dyspnoea ratings.

Conclusions: The COPD pathophysiology significantly varied among patients with different exercise capacities. Patients with lower exercise capacity suffered from severe gas exchange disorder, sympathetic overactivation, and ventilatory disturbance during exercise. CPET should consistently be performed to assess the factors that contribute to exercise limitation in COPD patients.

P1535 Inspiratory muscle training (IMT) with normocapnic hyperventilation (NH) improves respiratory muscle strength, exercise performance and ventilatory pattern in COPD patients
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Introduction: IMT by means of NH is effective in improving exercise endurance in healthy subjects but few data are available for COPD patients.

Aim: To evaluate the effect of 4 weeks NH training (Spirotiger®) on respiratory function and exercise capacity in 21 moderate/severe COPD patients.

Materials and methods: 19 M, 2 F; aged 42-80. Respiratory function tests (FEV1, FVC, Pimax), QoL (St George’s Questionnaire), 6MWT and endurance exercise performed at 75-80% of peak-work rate measured during an incremental test to the limit of tolerance (tLIM). 7 of 21 patients were instrumented with a portable inductive plethysmography (LifeShirt System) to evaluate breathing pattern during tLIM. After 1 month of weekly supervised training, the patients trained at home for 4 weeks: 10 min twice a day at a breathing rate 12-24/min with a tidal volume (TV) equal to 50% of CV.

Results: 6 patients dropped out (poor compliance). IMT significantly improved FEV1, Pimax, QoL. Exercise capacity. Ventilatory pattern after IMT is characterized by a significantly higher TV with no change in VE.

Table 1

<table>
<thead>
<tr>
<th>FEV1 (%)</th>
<th>FVC (%)</th>
<th>Pimax (kPa)</th>
<th>QoL (tLIM)</th>
<th>LIM (min)</th>
<th>6MWT (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>preIMT 55±16.9</td>
<td>82±12.8</td>
<td>28±16.6</td>
<td>4.0±0.4</td>
<td>436±74.5</td>
<td>postIMT 57±15.8</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>SpO2mean (%)</th>
<th>VE(L/min)</th>
<th>TV (L/min)</th>
<th>Br (b/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>preIMT 91±2.2</td>
<td>28±16.1</td>
<td>0.8±0.4</td>
<td>3±1.2</td>
</tr>
<tr>
<td>postIMT 92±3.5</td>
<td>29±16.4</td>
<td>0.9±0.4</td>
<td>30±8.6</td>
</tr>
</tbody>
</table>

*p<0.05 (statistical analysis: T test and Wilcoxon signed rank test).

Conclusion: After a short IMT with NH, COPD patients show a higher exercise capacity and an intriguing change in ventilatory pattern which improves oxygen saturation.
of patients during AECOPD. The aim of this study was to evaluate the impact of decreased blood hemoglobin level to results of six minute walking test in patients during after AECOPD.

Materials and methods: A retrospective analysis of data collected from long term study on AECOPD was performed. Haemoglobin level from the first obtainable hospital measurement was included in the assessment. 6MWD was performed after clinical improvement of the patient. Dyspnea at baseline and after exercise was measured. Oxygen saturation (SpO2) during exercise was measured.

Results: 404 patients with AE COPD were analyzed. GOLD stages, hemoglobin level and results of 6MWD are shown in Table 1. Results are means ±SD. *p<0.05. The hemoglobin level did not correlate with 6MWD, dyspnea after 6MWT, exercise oxygenation and blood desaturation after exercise.

Conclusion: Decreased blood hemoglobin level didn’t influence the results of 6MWT in patients after AECOPD.

P1537

Association between physical activity and asthma exacerbations
Silvia Pascual1, Isabel Urrutia1, Cristobal Esteban 1, Aitor Ballaz 1, Association between physical activity and asthma exacerbations was divided into quartiles, including 88 (24.8%) in the first quartile, 92 (25.7%) (11%) between 60 and 80%, and 300 (85%) greater than 80%. Physical activity was greater in those patients with higher exacerbations.

Introduction: There are some evidences that suggest that regular physical activity reduces the risk of exacerbations in asthma, regardless of the asthma severity and other factors. The aim of this paper is to measure the association between physical activity levels in asthma exacerbations, adjusted by FEV1, age and body mass index (BMI).

Methodology: This is a multicenter transversal study where has been included a population of asthmatic patients consults of two hospitals in Vizcaya. It has been included patients with previous diagnosis of asthma and monitored by the pneumologist at least for a year, aged between 18 and 70. We used the International Physical Activity Questionnaire (IPAQ). We performed a multivariate logistic regression analysis to determine predictors of exacerbations.

Results: We studied 354 patients (54% men). 115 of these (32%) were younger than 32, 123 (35%) between 32 and 55 and 116 (33%) over 55 years. 250 patients in the second, 54 (23.7%) in the third and 89 (25.1%) in the fourth.

Patients Number of pts GOLD stage 6MWD Age SpO2 before 6MWD Dyspnea after 6MWT Desaturation
(%) (m) (years) (%)
Anemic
N=105, 26% 3.4±0.7 258.1±125.1 74.5±8.2* 94±6.2 2.5±2.5 2.9±2.6
Non-anemic N=297, 74% 3.5±0.6 271.3±136.0 70.2±6.7* 93.9±3.1 2.2±2.4 3.6±3.7
All 402 3.5±0.6 265.6±132.5 71.5±8.8* 94.1±2.8 2.3±2.5 3.6±3.4

Conclusions: Patients with asthma with increased physical activity had a reduced number of exacerbations.

P1538

The usefulness of ventilatory gas analysis during low intensity exercise to define pulmonary hypertension
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The 6-minute walk test is widely utilized to characterize activity tolerance and response to therapy in pulmonary arterial hypertension (PAH). However, it provides little information about cardiopulmonary pathophysiology. Previous studies employing maximal exercise testing suggest that ventilatory gas analysis may be a useful tool to help determine the presence and severity of PAH. The aim of the present study was to determine whether measures of pulmonary gas exchange during a simplified low intensity step test can be used to differentiate between PAH patients and healthy individuals, and also stratify disease severity. Forty PAH patients and 25 matched controls completed a novel submaximal exercise test that consisted of 2-min rest, 3-min step exercise and 1-min recovery. Ventilation, pulmonary gas exchange, arterial oxygen saturation (SaO2) and heart rate were measured throughout using a simplified gas analysis system. A number of gas exchange variables separated PAH patients from controls. End-tidal CO2 (PETCO2) and SaO2 were lower in PAH vs. controls (31.4±7 vs 39.6±5 mmHg and 89±5 vs 95±2%, respectively, p<0.05) while breathing efficiency (VE/VCO2 ratio) was higher in PAH vs. controls (42±10 vs 33.5±3, p<0.05). PETCO2 and V/C02 also discriminated between different severities of PAH. Gas exchange variables obtained during light exercise clearly discriminated PAH patients from healthy controls and also between different severities of PAH. A simplified submaximal step test incorporating non invasive gas exchange may be a useful measure to help quantify and track disease severity in PAH. This study was supported by Gilead and NH HL71478.

P1539

Cardiac biopompeo during exercise testing in patients with idiopathic pulmonary arterial hypertension
Ralf Kaiser, Christian Frantz, Kerstin Hausdach, Christian Lench, Robert Bals, Heinrike Wilkens. Inneren Medizin V, University Hospital Saarland, Homburg/Saar, Germany

Purpose: In idiopathic pulmonary arterial hypertension (IPAH) right ventricular insufficiency develops due to pressure overload. Furthermore left ventricular function is reduced by chronic underfilling.

Hemodynamics are monitored by echocardiography and cardiac catheterisation. This may describe cardiac function only insufficient, as hemodynamics may change during exercise and balance between right and left ventricular function might change due to development of a septal shift. Recent studies have determined the importance of a simplified low intensity step test incorporating non invasive gas exchange may be a useful measure to help determine the presence and severity of PAH. The aim of the present study was to determine whether measures of pulmonary gas exchange during a simplified low intensity step test can be used to differentiate between PAH patients and healthy individuals, and also stratify disease severity. Forty PAH patients and 25 matched controls completed a novel submaximal exercise test that consisted of 2-min rest, 3-min step exercise and 1-min recovery. Ventilation, pulmonary gas exchange, arterial oxygen saturation (SaO2) and heart rate were measured throughout using a simplified gas analysis system. A number of gas exchange variables separated PAH patients from controls. End-tidal CO2 (PETCO2) and SaO2 were lower in PAH vs. controls (31.4±7 vs 39.6±5 mmHg and 89±5 vs 95±2%, respectively, p<0.05) while breathing efficiency (VE/VCO2 ratio) was higher in PAH vs. controls (42±10 vs 33.5±3, p<0.05). PETCO2 and V/C02 also discriminated between different severities of PAH. Gas exchange variables obtained during light exercise clearly discriminated PAH patients from healthy controls and also between different severities of PAH. A simplified submaximal step test incorporating non invasive gas exchange may be a useful measure to help quantify and track disease severity in PAH. This study was supported by Gilead and NIH HL71478.

Conclusions: Patients with asthma with increased physical activity had a reduced number of exacerbations.

P1540

Effects of continuous vs. interval aerobic training on PetCO2 response during graded exercise test in patients with coronary artery disease
Eneas Rocco1, Danilo Marcelo Prado-1,2, Alexandre Silva1, Jaqueline Lazzati1, Pedro Borta1, Debora Rocco1, Amanda Campolins1, Carla Rosa1, Valter Flurlan1, 1Cardiorespiratory Rehabilitation, Amil- International Medical Assistance, São Paulo, Brazil; 2Rheumatology Department, University of São Paulo- Medical School, São Paulo, Brazil. 1Exercise Physiology, Santa Cecília University, Santos, São Paulo, Brazil

Background: Previous studies have demonstrated in patients with coronary artery disease (CAD) that lower values in end-tidal CO2 pressure (PetCO2) during graded exercise test (GET) have been associated with ventilation perfusion (V/Q) mismatch.

Methods: To evaluate the effects of the continuous (CT) and interval aerobic training (IT) on PetCO2 responses during GET in CAD patients and 2) examine the relationships between PetCO2 at ventilatory anaerobic threshold (PetCO2V AT) and cardiorespiratory parameters after interventions.

Results: Patients with IPAH tolerated less workload (54.3±37 vs. 177.4±40W). Ejction fraction (EF) at baseline was comparable to control. During exercise the increase of EF was diminished in IPAH (62.1±8 vs. 67.4±5%) and maximal cardiac index (CI) was significantly lower (5.2±2.0 vs. 9.0±3.3lm/min/m2). Enddiastolic volume (EDV) showed a trend to decreased values (102.9±41 vs 128.8±35lm/min), while stroke index was markedly reduced (53.5±17 vs. 72.0±15lm/min). Peakflow during exercise was decreased (387.7±125 vs 559.0±180lm/min/m2) as well as flow acceleration (ACI: 153.5±61 vs 217.1±71sec2).

Conclusions: In patients with IPAH, stroke volume and CI were reduced. The diminished filling is represented by reduced EDH, resulting in less increase of contractility as shown by reduced peak flow and ACI. Patients with IPAH were not able to compensate the lack of contractility by heart rate, resulting in lower CI. Left ventricular underfilling affects cardiac performance during exercise, and isotropic response is reduced in patients with IPAH.
P1541
Quantifying oscillatory ventilation during exercise in patients with heart failure

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Background: This study tested the validity of a data analysis scheme to quantify measures of oscillatory ventilation at rest and during exercise in heart failure patients.

Methods: Eleven patients (age=53.8±8.5, LVEF=17.4±5.4, NYHA Class=II/III) (15) were recruited. Ventilation (V̇e) and gas exchange were measured. Amplitude and period of oscillation in V̇e, tidal volume (Vt), end-tidal carbon dioxide (PETCO2), and oxygen consumption (VO2) were measured manually (MAN), using novel software which included a peak detection algorithm (PK), sine wave fitting algorithm (SINE), and Fourier analysis (FOUR).

Results: During PK, there were no differences between MAN and PK for amplitude of V̇e, PETCO2, VO2, or Vt. Similarly, there were no differences between MAN and SINE for amplitude of V̇e or Vt although PETCO2 and VO2 were lower with SINE (p<0.05). The PK demonstrated shorter periods for V̇e, PETCO2, and VO2 compared to MAN (p<0.05) whereas there were no differences in periods of oscillations between MAN and SINE or FOUR. During exercise, there were no differences between MAN and PK for amplitude of V̇e, PETCO2, VO2, or Vt. SINE demonstrated lower amplitudes for V̇e, PETCO2, and VO2 compared to MAN (p<0.05) although Vt was not different. PK demonstrated shorter periods for all variables (p<0.05) whereas there were no differences between MAN and SINE or FOUR for all variables during exercise.

Conclusion: These data suggest 1) PK consistently captures amplitudes but underestimates period, 2) SINE and FOUR consistently capture period although SINE underestimates amplitude. Thus, an optimal algorithm for quantifying oscillatory ventilation in HF might combine multiple analysis methods. NIH grants HL74178/HL2-RR024151

P1542
The pattern and timing of breathing during graded exercise test in systemic lupus erythematosus

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1Biomédica, Department of Respiratory Medicine, University of São Paulo Medical School, São Paulo, Brazil; 2Biomédica, Department of Obstetrics, University of São Paulo Medical School, São Paulo, Brazil

Background: Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease that affects all organs including the respiratory system. Abnormal control of breathing during maximal voluntary ventilation has been recently identified in this disease.

Purpose: To evaluate the pattern and timing of breathing at selected submaximal ventilatory stress in SLE.

Methods: Twenty consecutive women (age: 28.8±1.0 years) with SLE were selected and compared to an age and BMI matched group of 19 healthy women (CTRL) (age: 26.2±1.3 years). All of the subjects performed a progressive treadmill cardiopulmonary test until exhaustion. Data were analyzed at absolute isoventilation (40, 60 and 80 L/min).

Results: SLE presented lower relative aerobic fitness (VO2peak) (26.8±8.2 vs. 35.9±1.2 mL kg-1 min-1, p<0.001) than their healthy peers.

Ventilatory parameters at different absolute isoventilation

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>40 L/min</th>
<th>60 L/min</th>
<th>80 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE Control</td>
<td>40.0±3.8</td>
<td>23.4±2.5</td>
<td>8.7±2.9</td>
</tr>
<tr>
<td>SLE Control</td>
<td>23.6±1.9</td>
<td>21.8±2.7</td>
<td>28.8±2.7</td>
</tr>
<tr>
<td>CTRL (c)</td>
<td>20.5±0.1</td>
<td>21.7±0.1</td>
<td>31.2±0.0</td>
</tr>
<tr>
<td>CTRL (c)</td>
<td>17.8±0.1</td>
<td>1.1±0.0</td>
<td>15.1±0.1</td>
</tr>
<tr>
<td>V̇T/VT (L/s)</td>
<td>1.4±0.0</td>
<td>1.4±0.0</td>
<td>1.0±0.0</td>
</tr>
<tr>
<td>V̇E/V̇T</td>
<td>31.0±0.6</td>
<td>27.4±0.7</td>
<td>31.9±0.6</td>
</tr>
<tr>
<td>V̇E/PETCO2</td>
<td>29.0±0.8</td>
<td>34.2±0.6</td>
<td>30.5±0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE. PETCO2 response during graded exercise test

<table>
<thead>
<tr>
<th>VAT</th>
<th>PEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td>CT</td>
<td>37.5±0.6</td>
</tr>
<tr>
<td>IT</td>
<td>38.0±0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SE. *P<0.05 vs. preintervention (Two-way ANOVA).

Conclusion: These results demonstrated a thachypnoeic breathing pattern and shorter timing of ventilation in SLE woman during exercise. This suggests that the reduced aerobic capacity observed in SLE patients may be accompanied by ventilation-perfusion mismatches.

P1543
Utility of ergospirometry in the diagnosis of hyperventilation syndrome (HVS)

Angelica Tioni 1, André Nosed 2, Sofia Abdelkafi 2. 1Department of Pneumology, CHU Nancy, Nancy, France; 2Department of Pneumology, CHU Brugmann, Brussels, Belgium

The hyperventilation syndrome (HVS) is characterized by several somatic and psychological symptoms due to hypocapnia not secondary to any underlying organic disease. The purpose of the present study was to evaluate the place of exercise-induced hyperventilation in the diagnosis of HVS.

Twenty-three patients with normal spirometry, referred for suspicion of HVS on the basis of a Nijmegen’s questionnaire (score ≥23) were eligible. Asthma was documented in 15 patients. The mean score of anxiety by the Spielberg’s State-Trait Anxiety Inventory for Adults was 53.5 which are suggestive of moderate anxiety. During the hyperventilation provocation test (HVPT), at least two symptoms of Nijmegen’s questionnaire were reproduced in 14 patients. The mean level of PetCO2 at 2 baseline was 27.6 mm Hg and decreased to 15.2 mm Hg for a maximal ventilation of 57 l/min. No patient recovered the baseline level of PetCO2 at 5 min after the end of the HVPT (mean ratio PetCO2 after/before p ≤ 0.05). Exercise-induced maximal ventilation (VImax) was 52 l/min and was accompanied by a PetCO2 level of 35.8 mm Hg and an EqCO2 of 32 mm Hg. No significant difference in the ventilatory pattern (VEmax, PetCO2, EqCO2) was found between HVS group (n=8) and the asthma and HVS group (n=15). In conclusion, in our group of patients with HVS, with or without asthma, the hyperventilation during exercise did not induce abnormal reduction in PetCO2 or abnormal increase in EqCO2. Our results suggest that, unexpectedly, the exercise could be a therapeutic tool in the HVS. It could be hypothesized that anxiety plays a role in the genesis of symptoms at rest but not during exercise where the patient has to be concentrated on his effort.

P1544
Exercise capacity as an index of progress of lung disease among children and adolescents with CF

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Background: Spirometry, high resolution computed tomography (HRCT) and exercise testing provide additional information about lung disease among children with cystic fibrosis (CF). There is significant correlation between levels of aerobic fitness (VO2 peak) and survival rate.

Aim: To compare decline of exercise capacity, HRCT scores and lung function among children with CF over a period of two years.

Methods: Sixteen stable children and adolescents with CF, aged 8–19 years, performed spirometry and maximal incremental cardiopulmonary exercise testing using a cycle ergometer, as part of their annual review. At the same time the patients underwent low dose of radiation chest HRCT scans, with a Bhalla score assessment.

Results: Sixteen stable children and adolescents with CF were evaluated (mean age 15.6±3.2 years and FEV1, 38.9±4% predicted). There was evidence of mild exercise limitation during the cardiopulmonary exercise test, with mean Peak Aerobic Capacity (V’Opeak) 71.8±14.0±7% predicted. Evaluation of the study population two years later, showed that Bhalla total score, Peak Aerobic Capacity (V’Opeak) and Anaerobic Threshold (AT) deteriorated significantly (mean difference ±SD, p: 1.4±1.7, p: 0.028, 6.4±1.1, p: 0.022, -7.8±9.3, p: 0.006, respectively). Ventilatory equivalent for CO2 (V’O2/VECO2), Dead space/Tidal Volume Ratio (VD/VT) and FEV1, didn’t deteriorate significantly (p: 0.321, p: 0.165 and p: 0.135, respectively).

Conclusions: The maximal incremental cardiopulmonary exercise test correlates well with HRCT scans; it is a very sensitive method for measuring progression of lung disease in children with CF.

P1545
Children with bronchopulmonary dysplasia (BPD) have increased dynamic flow limitation and an altered ventilatory response to exercise

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Introduction: Children born preterm are known to have altered lung structure and function. These changes may lead to dynamic flow limitation (DFL) during...
exercise. This study aimed to determine the prevalence of DFL and the ventilatory response to exercise in preterm children aged 9-11yrs with and without BPD.

**Methods:** Preterm children (<32 w gestation) with and without BPD (<28 d supplemental oxygen at 36 w post menstrual age) and term born healthy controls performed an incremental treadmill exercise test to volitional exhaustion with breath by breath analysis and exercise tidal flow volume loops.

**Results:** Of 89 children (33 BPD, 25 nonBPD and 31 controls) performed acceptable exercise tests. Children with BPD were more likely to have DFL (n=15, 36%) compared to nonBPD (n=3, 1%) and term controls (n=2, 6.3%) p<0.05. The pre-term children had a significantly lower peak V\textsubscript{O2} than the term born controls (43.8 ± 9.8 mL/kg/min, p<0.01). Children with BPD had a reduced O\textsubscript{2} pulse (p<0.001), tidal volume and V\textsubscript{E} (p<0.001) compared to nonBPD and term controls. Preterm children with dynamic flow limitation had lower FEV\textsubscript{1} z-scores compared to those without (p<0.02) with other ventilatory responses to exercise not altered in the presence of DFL.

**Conclusion:** Children born preterm have a lower aerobic exercise capacity and those with BPD exhibit both cardiac and respiratory limitation to exercise. The presence of DFL in children born preterm with BPD is a novel finding and further research on its potential impact is required.

P1546
Consequences of obesity on gas exchange during exercise
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Obesity produces an increment in total blood volume and cardiac output and a decrease in lung compliance as a result of increased pulmonary blood volume and alveolar collapse in the lung base.

**Aim:** To evaluate gas exchange parameters under incremental exercise in ‘healthy’ obese patients (pts).

**Methods:** Analysis of symptom limited incremental cardiopulmonary exercise tests in supine position of 115 pts (36M, 79F) with FEV\textsubscript{1}VC and TLC > 80% predicted (ECCS) and without history of cardiovascular disease. Pancuts of arterial radialis were made to evaluate arterial oxygen and carbon dioxide pressure (PaO\textsubscript{2}, PaCO\textsubscript{2}) at peak exercise (PE) and in-calculation of PaO\textsubscript{2} and alveolar-arterial oxygen pressure difference (PaO\textsubscript{2A} difference).

Slope of heart rate to oxygen uptake (DHR/DVO2 heat. l/min) was determined. Pts were divided into 2 groups: Ob (n=88): Body mass index (BMI) ≥ 30Kg/m\textsuperscript{2}, N (n=57): BMI < 30Kg/m\textsuperscript{2}.

**Results:** Significant differences were found between group Ob and N at PE in PaO\textsubscript{2} (83.3 vs 89.1mmHg, p<0.01) and PaCO\textsubscript{2} (36.4 vs 32.0mmHg, p<0.05), but no differences in heart rate (mean 161 ± 28 bpm, 104 ± 19 bpm, p<0.01), PaO\textsubscript{2} (mean 37.5 vs 37.6mmHg), and HR at peak (109 ± 16 vs 109 ± 16, p<0.05). These data indicate an increased extent of lung units with low ventilation/perfusion ratio (V/Q') but no differences in parameters of alveolar ventilation. Lowering of V'Q' ratio seems to be produced mainly by increase in lung perfusion.

**Conclusion:** Hypervolemia and pulmonary over-perfusion may be an important factor of gas exchange impairment under exercise in obese patients.

P1547
Oxygen saturation response during the six-minute walk test in patients with chronic respiratory disease
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Salut Mar-IMIM, Barcelona, Spain; 5FCS Blanquerna, GReF, Universitat Ramon Llull, Barcelona, Spain

Some guidelines recommend stopping 6-minute walk test (6MWT) if arterial oxygen saturation (SaO\textsubscript{2}) <85% as safety criteria. Our aim was to analyze the SaO\textsubscript{2} response <85% during 6MWT and its relation with clinical and symptomatic outcomes.

<table>
<thead>
<tr>
<th>SaO\textsubscript{2} (%)</th>
<th>(n=192)</th>
<th>(n=241)</th>
<th>(n=272)</th>
<th>(n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1} (l)</td>
<td>0.01</td>
<td>26.3±6.4</td>
<td>56.8±6.2</td>
<td>67.2±9.1</td>
</tr>
<tr>
<td>PaO\textsubscript{2} (mmHg)</td>
<td>0.005</td>
<td>61±10</td>
<td>69±10</td>
<td>75.6±11</td>
</tr>
<tr>
<td>Distance (m)</td>
<td>0.002</td>
<td>337±125</td>
<td>385±109</td>
<td>419±104</td>
</tr>
<tr>
<td>SaO\textsubscript{2} at rest (%)</td>
<td>0.001</td>
<td>91±5</td>
<td>94±2</td>
<td>96±1</td>
</tr>
<tr>
<td>SaO\textsubscript{2} max (%)</td>
<td>0.001</td>
<td>79±5</td>
<td>88±5</td>
<td>91±2</td>
</tr>
<tr>
<td>HR at rest (lpm)</td>
<td>0.001</td>
<td>91±12</td>
<td>84±14</td>
<td>84±14</td>
</tr>
<tr>
<td>HR max (lpm)</td>
<td>0.001</td>
<td>117±16</td>
<td>111±17</td>
<td>110±15</td>
</tr>
<tr>
<td>Dyspnea (Borg scale)</td>
<td>0.001</td>
<td>2.2±3</td>
<td>2.2±3</td>
<td>2.2±3</td>
</tr>
<tr>
<td>Fatigue end (Borg scale)</td>
<td>0.001</td>
<td>2.2±3</td>
<td>2.2±3</td>
<td>2.2±3</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SD.

**Methods:** Retrospectively, we analyzed 6MWT from two respiratory medicine services from tertiary hospitals: Hospital del Mar and Hospital Clinic, Spain, from 2006 to 2010. They did not stop 6MWT using SaO\textsubscript{2} <85% criteria. We analyzed the data in 4 groups according SaO\textsubscript{2}.

**Results:** 796 patients (68±10 years) were analyzed. The results of ANOVA are:

- Only 2 (0.5%) patients showed complications (leg pain and leg paresthesias) within groups (p=0.43). Few patients stopped during 6MWT in all groups (p=0.15).

**Conclusions:** Patients with SaO\textsubscript{2} <85% during 6MWT showed less distance walked and poor functional parameters. However, this group did not show differences neither in number of patients who stopped during the test nor presence of clinical complications during and after 6MWT. Our results confirm there are not critical effects in this kind of patients to stop the test using the SaO\textsubscript{2} <85% criteria.

164. Smoking-related disorders and smoking prevention

P1549
Exposure to environmental tobacco smoke in childhood is associated to lung function in smoking adults
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**Objective:** To analyse for associations between exposure to environmental tobacco smoke (ETS) in childhood and lung function in young adults.

**Methods:** In a Danish cross-sectional study of asthma in subjects aged 20-44 years (ERCHIS protocol) 690 randomly selected subjects were eligible for analysis. Information of the participant exposure to ETS in childhood was collected. The history and current exposure to ETS was based on questionnaire. FEV\textsubscript{1} and FVC were measured according to ERS and ATS recommendation.

**Results:** No ETS exposure in childhood was reported by 130 subjects, while 245 and 315 subjects reported one or two parents smoking at home, respectively. Mean FEV\textsubscript{1}/FVC ratio (95% CI) was 0.79 (0.789-0.805). ETS in childhood had negative effect on the FEV\textsubscript{1}/FVC ratio (p=0.025 and p=0.001 by one or two parents, respectively). Stratifying for smoking habits the results were only significant among the 194 current smokers. Figure 1 shows relative difference in FEV\textsubscript{1}/FVC ratio in smoking adults by number of parents smoking at home in childhood stratified by the group, adjusted for gender, pack year, current exposure to ETS, study centre, and height.

281s
P1550

Environmental tobacco smoke (ETS) in allergic asthma: A parallel exposure study in human subjects and sensitized allergic Balbc mice

Introduction: The present study focused on the acute effects of short term (3 hours) exposure to ETS in allergic asthma, in a mouse model as well as in asthmatics.

Methods: Analogously 23 non-smoking asthmatics as well as 54 allergic challenged Balbc mice were exposed to artificially produced ETS in increasing concentrations (I=250 µg/m³, II= 450 µg/m³, III=850 µg/m³) to or ambient air (control group).

In human asthmatics, lung function, exhaled NO and exhaled CO was assessed. Serum samples were analyzed for cytokine profile and distribution of immune cells. Symptom severity was assessed via asthma control test (ACT) and visual analogue scale (VAS) questionnaires.

Whole body plethysmography was performed in mice before, after and one day after ETS exposure. The immunological status of mice was assessed by analysing serum cytokines and BALF cell composition.

Results: Human asthmatics exposed to ETS II and ETS III had significantly lower FeNO levels, a decrease in lung function of small airways (MEF25, MEF50) and an increase in VAS scores compared to controls. In sera ETS II led to a more anti-inflammatory cytokine profile (IL10) whereas ETS III showed a proinflammatory cytokine milieu (IL8, TNF-α) in human asthmatics.

Conclusion: The data indicate a direct and dose dependent effect of ETS exposure on lung function as well as respiratory inflammation in human asthmatics and sensitized allergic mice.

P1551

Smoking rates in pregnant women one year before and after the Irish workplace smoke-free policy: A widening gap?

Introduction: The role of the smoke-free legislation on emergency department admissions due to tobacco-related diseases in Kocaeli was evaluated retrospectively before and after the implementation of the Tobacco Prevention and Control Research Center, NRITLD, Tehran, Islamic Republic of Iran

Methods: A cross-sectional observational study using questionnaire based on WHO MPOWER guidelines was developed. A scoring system based on the Tobacco control scale methodology was used with total score of 100 in 6 major categories. Information about country was also collected from the WHO report and the Tobacco Atlas 2009 and the World Bank report of 2008.

Results: Among 21 Eastern Mediterranean countries, only 3 countries (14.2%) mainly Iran (61%), Jordan (55%) and Egypt (51%), scored higher than 50. Mean score for countries were 29.7±4.3 points. More than 50% of the countries scored less than 26. Highest scores were achieved by Afghanistan in cigarette pricing, Oman in smoking ban in public places, Iran in budgeting, prohibition of advertisement and health warnings against smoking and Yemen in tobacco cessations programs.

Conclusion: Countries in the EMRO region lack the ideal conditions for tobacco control and the related authorities are required to make changes and amendments in their policies for achieving desirable results.

P1554

The role of the smoke-free legislation on emergency department admissions due to tobacco-related diseases in Kocaeli

Introduction: Confusion by health organizations in the public debate on legal smoking ban in Switzerland

Background: Signature of the FCTC and the parliamentary initiative of MP Gutzwiller MD in 2004 started the process to a smoking ban, but resulted 10/08 in the federal Alibs Law, meeting neither international nor WHO standards. Thus, the Swiss Lung League (SLL; federation of cantonal lung leagues) launched an initiative with the collection of 130 000 signatures by 05/10. Media reporting is powerful only 10% of articles in the period 02/10 were positive on smoking bans; so pressure on MPs is insufficient to improve legislation.

Aim: To detect communication flaws contributing to poor media reporting.

Method: Analysis of official positions by health organizations on passive smoking.

Results: A. The PMH (Federation of Swiss physicians) declined (letter 03/09), but finally backed 01/10 the SLL-initiative. B. The president of the the Society of Internists (SSI), declined positioning on passive smoking at its assembly 2008, arguing the congress was not nonsmoking and sponsors should be consulted (letter 04/08). The SSI has not positioned itself yet (submission) on its support of the SLL initiative. C. By its launching the SLL urged cantonal lung leagues to collect signatures. Some cantonal leagues did not (e.g. Zurich, Vaud). Despite initial desaprobation by the lung league Vaud (letter 12/08), the annual report 2009 of this league declared official support of the SLL initiative.

Conclusion: Reports on smoking bans are likely to improve, if health organizations communicate in a coordinated way. This can be achieved by all health organizations, since toxicity of passive smoke and public health benefits of smoking ban in public places are based on sound scientific evidence.

P1553

Comparison of tobacco control policies in the eastern Mediterranean countries based on tobacco control scale scores

Conclusion: Working separately for each of the two calendar years.

Results: data on January to June 2009 and 2010 were compared for the prevention of lower respiratory tract infections (LRTI), allergic rhinitis (AR) and myocardial infarction (MI) were recorded. The number of admissions to emergency departments of 15 hospitals due to tobacco-related diseases before and after smoke-free legislation.

Aim: The aim of the study was to evaluate the admissions to emergency department due to tobacco-related diseases before and after smoke-free legislation.

Method: The number of admissions to emergency departments of 15 hospitals in Kocaeli was evaluated retrospectively before and after the implementation of smoke-free legislation published on 19 July 2009. ICO codes of smoking-related disease which were determined as bronchitis (BR), chronic obstructive pulmonary disease (COPD), asthma, nasopharyngitis (NP), lower respiratory tract infections (LRTI), allergic rhinitis (AR) and myocardial infarction (MI) were recorded. The data on January to June 2009 and 2010 were compared for the prevention of seasonal changes.
Results: There was a 22.5% decline in all emergency admissions due to smoking-related diseases.

Total number of admissions due to above mentioned diseases was 83,089 in the first 6 months of 2009 while it was decreased to 64,314 in the first 6 months of 2010. There was a 39.8% reduction in the diagnosis of bronchitis, 4.3% of reduction in the lower respiratory tract infections, 61.9% reduction for allergic rhinitis and 21.5% reduction in the COPD exacerbations. Conclusion: The number of admissions to emergency department due to tobacco-related disease decreased after the implementation of smoke-free legislation. This finding might be interpreted as an achievement of smoke-free environment.

P1555
Tobacco smoking and cardiovascular parameters
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The aim: To study the influence of tobacco smoking on cardiovascular parameters. Methods: A total of 200 smokers were examined (index of smoking≥5 packs/years). The mean age was 42.7±7.57 years. The acute tests were carried out: the first one was smoking 1 cigarette, then after 24 hours the 2nd test was smoking 2 cigarettes. The parameters were studied before and after smoking 1 and 2 cigarettes: diameter of a humeral artery, pulsioxymetry, Holter monitoring ECG.

Results: Diameter of a humeral artery in ten minutes after smoking 1 and 2 cigarettes decreased by 5.48% (2.4-8.9) and 6.89% (2.96-10.23), accordingly, p<0.05. Diameter of a humeral artery in fifteen minutes after smoking 1 and 2 cigarettes decreased by 6.25% (3.7-9.9) and 8.29% (3.42-12.58), accordingly, p<0.05. Diameter of a humeral artery in twenty minutes after smoking 1 and 2 cigarettes decreased by 6.71% (3.79-10.9) and 8.6% (5.11-12.78), accordingly, p<0.003. The oxygen saturation of blood before smoking cigarettes was 98% (96.98) of predicted; 10 minutes after smoking 1 cigarette it was 96% (95.98) (p<0.0001), 15 minutes after-99% (94.98) (p<0.0001), 10 minutes after smoking 2 cigarettes it was 96% (94.98) (p<0.0001), 15 minutes after-96% (94.98) (p<0.0001), 20 minutes after-90% (94.98) (p<0.001). Heart rates (HR) before smoking cigarettes were 78±130; one minute after smoking 1 cigarette it was 94±113 (p<0.0001), after two minutes-88±12 (p<0.0001); one minute after smoking 2 cigarettes it was 98±114.5 (p<0.0001), after two minutes-89±15.2 (p<0.0001), after three minutes-83±112.9 (p<0.03).

Conclusion: Tobacco smoking can cause significant changes of cardiovascular parameters. The smoking of 2 cigarettes gives more distinctive changes in cardiovascular parameters.

P1556
Does smoking impair the quality of life of 34 year olds with alpha-1 antitrypsin deficiency?
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Background: Alpha-1 antitrypsin (AAT) protects lung tissue against degradation. Hereditary AAT deficiency increases the risk of pulmonary emphysema. During Alpha 1-antitrypsin (AAT) protects lung tissue against degradation.

Background: This study included 129 PiZZ and 55 PiSZ individuals, and 300 age cohort of individuals with AAT deficiency at the age of 34. Identified. We have examined whether smoking affects the quality of life in the participants. Low scores indicate better quality of life in a 0-100 scale in response to the SGRQ questionnaire.

Results: The students were classified in 3 groups: G1, never smokers (n=1283; men=595; age=16±1.1 years); G2, subjects who have experimented smoking at least once in their lives (n=487; men=224; age=16.3±1.1 years), and G3, current smokers (n=244; men=128; age=16±1.1 years). The mean PSS for G1 (16.5±6.4) was significantly lower than that of G2 (18.0±6.8) and G3 (19.2±6.7) (p<0.001). There was a non-significant difference between G2 and G3 regarding PSS (p=0.05). There were significant correlations between PSS and the following USP-RSS domains: addiction (p=0.015; r=0.161), tension reduction (p=0.0002; r=0.243), stimulation (p=0.013; r=0.164), automatism (p=0.020; r=0.154). Weight control showed only a marginally significant correlation (p=0.052; r=0.130).

Conclusion: Stress levels in teenagers appear to contribute to the smoking experiment. However, it has not to the addiction establishment. Stress levels show small, but significant, correlations with important factors that contribute to smoking maintenance. Supported by: FAPESP 09/5052-0.

P1557
Stress influence on smoking behavior of teenagers
Amanda Bomtilha1, Elisa Souza1, Antonio Ruffino Netto2, Jose Baddini Martinez1. 1Internal Medicine, 2Social Medicine, Medical School of Ribeirão Preto - USP; Ribeirão Preto, São Paulo, Brazil

Rationale: Previous studies suggested that stress levels might influence smoking behavior.

Objectives: To investigate the stress levels among teenagers according to their smoking history. To correlate stress levels with health outcomes. To evaluate the effectiveness of mucociliary clearance (MCC) and to development of mucociliary insufficiency in patients with chronic non-obstructive bronchitis.

Methods: We recruited a thousand and fourteen high school students and afterwards they answered a standard questionnaire including the Perceived Stress Scale (PSS) and the USP-RSS. Comparisons among scores were performed by ANOVA on ranks and Dunn’s post test when indicated. Associations between USP-RSS domains scores and PSS scores were performed by Spearman’s correlation coefficient.

Results: The students were classified in 3 groups: G1, never smokers (n=1283; men=595; age=16±1.1 years); G2, subjects who have experimented smoking at least once in their lives (n=487; men=224; age=16.3±1.1 years), and G3, current smokers (n=244; men=128; age=16±1.1 years). The mean PSS for G1 (16.5±6.4) was significantly lower than that of G2 (18.0±6.8) and G3 (19.2±6.7) (p<0.001). There was a non-significant difference between G2 and G3 regarding PSS (p=0.05). There were significant correlations between PSS and the following USP-RSS domains: addiction (p=0.015; r=0.161), tension reduction (p=0.0002; r=0.243), stimulation (p=0.013; r=0.164), automatism (p=0.020; r=0.154). Weight control showed only a marginally significant correlation (p=0.052; r=0.130).

Conclusion: Stress levels in teenagers appear to contribute to the smoking experimentation. However, it has not to the addiction establishment. Stress levels show small, but significant, correlations with important factors that contribute to smoking maintenance. Supported by: FAPESP 09/5052-0.

P1558
Predictive role of smoking in the development of mucociliary insufficiency in patients with chronic non-obstructive bronchitis
Victor P. Kolosov, Andrey N. Odareev, Artem V. Kolosov. Laboratory of Pathophysiology of Non-specific Lung Diseases, Scientific Center of Physiology and Pathology of Respiration, Blagoveschensk, Russian Federation

Background: Smoking in patients with chronic bronchitis can lead to decrease of effectiveness of mucociliary clearance (MCC) and to development of mucociliary insufficiency at the early stages of a disease formation. Aim: To study the peculiarities of mucociliary system functioning in patients with chronic obstructive bronchitis but not to the addiction establishment. Stress levels show small, but significant, correlations with important factors that contribute to smoking maintenance. Supported by: FAPESP 09/5052-0.

Methods: Spirography, the study of MCC by scintigraphy with 99mTc, the study of effectiveness of mucociliary clearance (MCC) and to development of mucociliary insufficiency in patients with chronic non-obstructive bronchitis (CNOB) with latent smoking history. To correlate stress levels with scores of the University of São Paulo-RSS domains, including the Perceived Stress Scale (PSS) and the USP-RSS. Comparisons among scores were performed by ANOVA on ranks and Dunn’s post test when indicated. Associations between USP-RSS domains scores and PSS scores were performed by Spearman’s correlation coefficient.

Results: The students were classified in 3 groups: G1, never smokers (n=1283; men=595; age=16±1.1 years); G2, subjects who have experimented smoking at least once in their lives (n=487; men=224; age=16.3±1.1 years), and G3, current smokers (n=244; men=128; age=16±1.1 years). The mean PSS for G1 (16.5±6.4) was significantly lower than that of G2 (18.0±6.8) and G3 (19.2±6.7) (p<0.001). There was a non-significant difference between G2 and G3 regarding PSS (p=0.05). There were significant correlations between PSS and the following USP-RSS domains: addiction (p=0.015; r=0.161), tension reduction (p=0.0002; r=0.243), stimulation (p=0.013; r=0.164), automatism (p=0.020; r=0.154). Weight control showed only a marginally significant correlation (p=0.052; r=0.130).

Conclusion: Stress levels in teenagers appear to contribute to the smoking experiment. However, it has not to the addiction establishment. Stress levels show small, but significant, correlations with important factors that contribute to smoking maintenance. Supported by: FAPESP 09/5052-0.
respiratory function test. Patients presenting normal respiratory function and with CT-detected pulmonary emphysema (PE) are not diagnosed as having COPD. As surfactant protein D (SP-D), human β-2-defensin 2 (HBD2), and intercelleukin-8 (IL-8) have been reported as serum markers of COPD, they may be useful for the diagnosis of CT-detected PE.

Aim: The aim of this study was to investigate the usefulness of serum markers (SP-D, HBD2, and IL-8) for patients with COPD and CT-detected PE.

Method: A total of 326 subjects were screened. Of these, 55 were excluded because they failed to meet the criteria for this study, leaving 271 subjects for analysis. They underwent a respiratory function test and chest CT. According to the results, the subjects were classified into four groups: control group (n=40), non-COPD group (n=169), CT-detected PE group (n=42), and COPD group (n=20). Serum marker (HBD2, SP-D, and IL-8) levels were measured by ELISA and evaluated.

Result: Serum SP-D levels in the CT-detected PE group (66.3 ± 31.6 ng/ml), and in, in comparison with the non-COPD group (49.3 ± 32.9 ng/ml) showed a significantly different elevation (p=0.026). However, there were no significant differences serum IL-8 and HBD2 levels among the four groups.

Conclusion: This study suggests that serum SP-D level might be a useful marker for detecting CT-detected PE.

P1560 Widening inequalities in smoking rates in the Republic of Ireland?
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Methods: Complete smoking-related information on adults (≥18 years) for 1998 [n=25,203] and 2007 [n=21,051] were analysed. Age-standardized smoking rates for each of the two main indicators were computed overall and by sex using 2002 Census as the standard population. Relative index of inequality (RII) in age-standardized smoking rates was computed (comparing the lowest with the highest socio-economic groups) for each calendar year based on relative ranking (0=highest; 1=lowest) and then regressing the cumulative percentile distribution of the sub-classes within each year 95% confidence intervals (CI) for RII were generated.

Results: Overall, sample-weighted smoking rates declined from 33% (in 1998) to 29% (in 2007). However, the lowest SC groups recorded 51% higher smoking rates compared to the highest SC groups in 1998 and this widened relatively by 37% (2007) among those with lowest education widened relatively by 40% (from 35% to 49%) between the two time-periods compared to the highest groups. Female smoking rates have increased more relative to their male counterparts in lower SC groups.

Conclusions: Overall, smoking rates have declined in Ireland over a 10-year period but using “a” relative index of inequality measure, social inequalities in smoking rates have significantly widened in lower socio-economic groups, worsening further among disadvantaged females. Tobacco control policies combined with socio-economic interventions are imperative to address these inequalities.

P1561 Smokeless tobacco use among young male adults in northern Finland
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Background: Smokeless tobacco (ST) sales have been banned in Finland since 1995 while its’ import for own personal use is allowed. Despite the sales ban, adolescents and young adults use ST. According to a national survey in 2009, 41% of 18-year-olds had experimented smokeless tobacco and 2.1% used it daily, and the trend seems to be increasing [1].

Aims: To study Swedish moist snuff use among young adult males in Northern Finland with fairly close access to Sweden, where ST products are available.

Methods: Data was collected during 2008-2009. The study population consists of 1151 male military recruits from the two most northern regions of Finland (mean age 19.4, 94.2% 18-20 years). All draftees were applied to answer a specific questionnaire. Response rate was high, 80%.

Results: Most young males (70.4%) had experimented ST at least once. Current daily ST use was reported by 14.3%, and 28% reported occasional use. Among daily users, mean duration of ST use was 3-0 years.

Conclusions: Despite the sales ban in Finland, ST use is common among young adult males. Compared to national prevalence, daily ST use was high in Northern Finland where also smoking is relatively common [2]. This might relate to cultural differences inside the country, but also to easy snus availability in the northern parts of the country.

References:

P1562 Phenotypic features in COPD smokers attending a smoking cessation unit
Carlos A. Jimenez Ruiz, Ana Maria Cicero Guerrero, Maria Luisa Mayayo Ulbarri, Maria Isabel Cristobal Fernandez, Genia Lopez Gonzalez. Unidad Especializada Tabaquismo, Salud Madrid, Madrid, Spain

COPD smokers have specific features of their smoking habit. We reviewed medical histories of all COPD patients who were treated in our Unit between January 2004 and January 2010. Medical and smoking histories were obtained during the baseline visit, as well as different test results such as FTND-questionnaire, Reward Test and Test to measure psychological, social and gestual dependence.

These test results obtained were compared with those of a historical group of non-COPD patients treated in our Unit (Control Group). 472 COPD smokers showed the following data for gender (65% were male), average age 58.3 (9.8), number of cigarettes per day 29.7 (13.4), number of years smoking 40.5 (9.9) and number of pack-years 59.1 (30.2). For the control group, which consisted of 1850 patients, these data were 50% male, 47.8 (11), 28.3 (10.4), 32.3 (11.5) and 45.8 (25.7), respectively.

The average score on FTND-questionnaire was 7.4 (2.1) for COPD patients, against 6.5 (2.4), p<0.001 in the control group. 79% of COPD smokers were a negative reward smokers, against a 56% of the control group, p<0.01. COPD patients had a low rate on gestual and social dependence, as well as on automatism. On the contrary, they had a high rate on psychic dependence and sedation.

COPD smokers who attend a smoking cessation unit are generally male over 55 years old, have higher figures of years smoking and higher pack-year figures than the control group. Their physical nicotine dependence is higher than for those in the control group. They are negative reward smokers more often and more significantly than those in the control group.

COPD smokers have a low grade of gestual and social dependence and a high grade of psychic dependence.

P1563 Prevalence and predictors of smoking cessation rates in Ireland: A follow-up cross-sectional study
Sheila Keoghan1, Zubair Kabir1, Laura Currie1, Miriam Gunning2, Paula Campbell1, Luke Clancy 1, 3 Research, TobaccoFree Research Institute, Dublin, Ireland; 2Health Promotion Office, Health Service Executive, Dublin, Ireland

Background: We reported that intensive smoking cessation (SC) services are available in Ireland but lack uniformity or consistency countrywide [1]. Here we estimated successful quit rates at 4-weeks and again at 3-months follow-up relative to baseline after setting up a quit date, and identified significant predictors of quitting at 4-weeks follow-up relative to baseline smoking status.

Methods: A convenience sample of 1,490 patients was recruited while attending SC service throughout Ireland. An electronic database was created. Intention-to-treat analyses were performed employing stepwise multivariable logistic regression modelling to identify significant predictors from several covariates for which complete data were available. Smoking status was self-reported. Carbon monoxide (CO) monitoring was done but was patchy.

Results: 37% had quit smoking at 4-weeks after setting up a quit date (p<0.001) and a lower proportion (22.4%) quit smoking at 3-months follow-up (p<0.001). Only occupation [professionals had 58% increased success rates relative to semi/unskilled] and client sources [outpatients were least likely to succeed] were significant predictors (p<0.05) of SC rates at 4-weeks follow-up.

Conclusions: This pilot study demonstrated that SC services if avaliable of could result in quitting when followed-up both at 4-weeks and at 3-months, despite attrition. A cost-effective comprehensive tobacco dependence treatment program can accelerate further declines in smoking rates.

Reference:
213. Understanding the burden of chronic respiratory diseases: what decision makers need to know

1677 Sporimetric screening and survey of knowledge on COPD and smoking in Spanish political representatives: The ConSePOC study

Methods: 50 improvement projects focussed on different steps of the pathway: outcomes.

across the whole care pathway.

of the national COPD strategy and enables delivery of effective clinical practice testing approaches to develop and refine news ways of working.

service improvement tools, each project used data to form objective measures of effective self management, managing high impact users, structured patient reviews, effective care models are early accurate diagnosis, medicines optimisation, effec-

alised cost efficiency saving of £590k. Other emerging principles that underpin assessment and review, 7 home oxygen projects have demonstrated a total annu-

Results: Prevalence of COPD stage I was 12%, and 5% for stage II+. Resource use in stage II+ categories was significantly higher in COPD patients than in control subjects.

8 results were calculated from utilization by applying national unit costs. To control for confounders such as age, sex and education, two-part generalized regression analyses were used to account for the skewed distribution of costs and the high proportion of subjects without any costs.

8 conclusions: The finding that resource use and costs are considerably higher in moderate but not in mild COPD highlights the economic importance of prevention programs and of interventions aiming at early diagnosis and at delaying disease progression.

1680 The impact of a respiratory in-reach service into the emergency assessment unit (EAU) on treatment, length of stay, and re-admission rates

Background: Respiratory illness is the second commonest reason for admission to hospital in the UK. Specialist input leads to better outcomes and reduced length of stay. Approximately half of respiratory patients, at New Cross Hospital, Wolverhampton, are not reviewed by a specialist during their admission.

Aims: The aim of this study was to assess whether addition of specialist respiratory input into the EAU, would optimise patient management, and thus reduce length of stay and re-admission rates.

Methods: During the weekday working hours, we piloted a twice daily respiratory ward round in the EAU. We audited management against current BTS guidance, identifying treatment where required. We compared length of stay and re-admission rates during the pilot month to that of the preceding month. We collected data on whether patients would have been appropriate for referral to a respiratory “hot clinic”, to assess the need and demand for this service in the Wolverhampton City PCT.

Results: 73.1% of patients had management altered, according to BTS guidance. 53.7% of patients had undergoing respiratory disease on admission, and of these, only 50% were optimally treated according to guidance. Re-admission rates decreased by 13.4% and length of stay decreased by 1.38 days. 25% of patients could have been seen in a “hot clinic”, preventing a hospital admission.

Conclusion: There is a role for the addition of a respiratory specialist ward round in the EAU of New Cross Hospital, to optimise management of patients with respiratory illness, and to reduce patient length of stay and re-admission rates.

1681 The economic burden of COPD in a Danish municipality

The economic burden of chronic diseases are a great challenge to our future welfare. The purpose of this study was to create a qualified measurement of the expenses to COPD in a Danish Municipality and determine the division of these between the Municipality and the Government.

From the National Patient Register patients with COPD, Diabetes and Cardiovas-

cular diseases living in the Municipality of Helsingør (61,295 inhabitants) were
Cost-effectiveness of tiotropium versus salmeterol: A trial-based analysis followed by a model-based extrapolation

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Background: The 1-year POET trial compared tiotropium to salmeterol regarding the effect on COPD exacerbations. Data from that trial informed this cost-effectiveness analysis (CEA).

Aim: Performing a 1-year trial-based CEA of tiotropium versus salmeterol, followed by a 5-year model-based CEA, from the perspective of the German Social Health Insurance in 2010.

Methods: The within-trial CEA included 7250 patients that had resource utilization recorded (COPD-related drug use and exacerbation-related healthcare use). The trial-based analysis was followed by a model-based analysis to synthesize the POET results with evidence from earlier studies, extrapolate results to 5-years, include costs of COPD maintenance treatment, and adapt to the severity distribution of the German population. Main endpoints were difference in costs, number of exacerbations, and quality-adjusted life-years (QALYs; model only).

Results: One-year costs were €1089 and €963 per patient treated with tiotropium and salmeterol, respectively, a difference of €126 Euro (95% uncertainty interval (UI): 55-195). The number of exacerbations avoided due to tiotropium was 1089 and 1089 for the endpoints exacerbation avoided and QALY, respectively. Following the extension to 5 years, the latter ICER changed to €3488.

Conclusion: Tiotropium reduced exacerbation-related costs, generating an incremental cost-effectiveness ratio (ICER) that is considered cost-effective.

Clinical and pharmacy-economical reasonability of the choice of fixed combination of fluticasone/salmeterol in the curing of bronchial asthma in the country with limited financing of the public health

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Aim: To estimate the real practice of prescription of preparations in curing BA, to analyze clinical and pharma-economical efficiency of conversion to the fixed combination of SALMFP in curing BA.

Method: The real practice of curing 266 patients with separated using of different preparations of basic therapy and short-rated broncholitics was retrospectively analyzed during the year (1st period) and the following year of their using of SALMFP (2nd period).

Results: It was managed to attain control (ACT) of 15.5% of patients in the real practice (1st period). System glucocorticoids were ambulatorially prescribed to 41 patient. On the average each patient used 15.6 inhaler SABA. The cost of treatment (ambulant hospitalization, medications, visits of the doctor, social payment) came to 1405 EUR per year.

Conclusion: The real clinical practice of curing BA in RB often differs from the recommendations of GINA 2009 and leads to the low level of control of BA (among 15.5%). The conversion to using fixed combination of SALMFP enables to increase the percentage of patients with controlled asthma to 74.3%, and cut the cost of treatment by 1.6 times.

Mechanisms of acute lung injury and mesenchymal cell treatment

1682

A late-breaking abstract: Soluble immune complex exaggerates LPS-Induced acute lung injury (ALI) by transfusion – A novel mechanism of transfusion-related acute lung injury (TRALI)

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Rationale: TRALI is a major cause of morbidity and mortality related to transfusion therapy. Soluble immune complex (ICs) could aggravate LPS-induced lung injury. We speculate that ICs formation during transfusion may play a role in the pathogenesis of TRALI.

Aim: To design a double-hit mice model to simulate TRALI development. The first hit is LPS i.t. injection. The second hit is transfusion of conditioned blood 24 hours after LPS injection. Mice were sacrificed 6 hours later. The conditioned blood was generated by transfusing 0.1cc/day CS7 mouse blood to BALB/c mice consecutively for two weeks.

Methods: A 2-hit model of BALB/c mice was used. Animal were divided into four groups XX, XB, LP and LB: (X: no treatment, L: LPS i.t.; B: transfusion of conditioned blood, P: transfusion with PBS). The body weight, clinical symptoms, blood pressure, liver and lung tissue were observed.

Results: The LB group has higher protein, TNF-α and MIP-2 level in BALF.

Table 1. BAL fluid

<table>
<thead>
<tr>
<th>Group</th>
<th>X (n=5)</th>
<th>BB (n=5)</th>
<th>LP (n=9)</th>
<th>LB (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell count (10⁶)</td>
<td>0.73±0.21</td>
<td>0.73±0.17</td>
<td>3.74±1.20</td>
<td>4.70±1.25</td>
</tr>
<tr>
<td>Neut. (%)</td>
<td>1.40±0.75</td>
<td>0.50±0.22</td>
<td>59.8±13.2</td>
<td>70.6±10.6</td>
</tr>
<tr>
<td>Protein (μg/ml)</td>
<td>0.12±0.04</td>
<td>0.08±0.02</td>
<td>0.41±0.07</td>
<td>0.69±0.02*</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>42.0±16.8</td>
<td>78.2±17.7</td>
<td>473.0±53.2</td>
<td>680.0±158.6</td>
</tr>
<tr>
<td>MIP-2 (pg/ml)</td>
<td>21.0±5.2</td>
<td>31.1±12.7</td>
<td>348.5±84.3</td>
<td>871.2±186.7*</td>
</tr>
</tbody>
</table>

* p<0.05 as compared with LP.

2. Soluble ICs is present in LB only.

Table 2. ICs in plasma

<table>
<thead>
<tr>
<th>Group</th>
<th>X (n=5)</th>
<th>BB (n=5)</th>
<th>LP (n=9)</th>
<th>LB (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICs in plasma</td>
<td>0 / 5</td>
<td>0 / 5</td>
<td>1 / 9</td>
<td>8 / 9</td>
</tr>
</tbody>
</table>

Conclusion: We demonstrated that transfusion with 2cc conditioned blood aggravated LPS-induced ALI and generated soluble ICs in plasma. This probably indicates ICs may aggravate pre-existing ALI which implies a novel mechanism of the pathogenesis of TRALI.

1685

A haplotype of the endothelial protein C receptor gene is associated with reduced risk of acute lung injury in critically ill patients

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Aim: To investigate the role of PC gene as predisposing factor for ALI/ARDS.

Methods: Twenty ALI/ARDS patients with chronic respiratory disease were included in this study. A total of 1700 ng/ml of protein C was identified by ELISA. We detected rare mutations in the PC gene (c.1051C>G, c.1051C>A) associations with ALI/ARDS.

Results: Six patients with chronic respiratory disease were included in this study. A total of 1700 ng/ml of protein C was identified by ELISA. We detected rare mutations in the PC gene (c.1051C>G, c.1051C>A) associations with ALI/ARDS.

Conclusion: Our study indicate that PC gene rare mutations (c.1051C>G, c.1051C>A) may be associated with ALI/ARDS.

Mechanisms of acute lung injury and mesenchymal cell treatment

1684

A haptopy of the endotelial protein C receptor gene is associated with reduced risk of acute lung injury in critically ill patients

Akiha Vassiliou1, Nikolaos Mamatlis1, Anastasia Kouandis2, Eleftheria Letsyos1, Marina Kallergis2, Fotemi Karyntzaki2, Chisrina Sotropoulou1, Konstantinos Glynos1,2, Ioanna Dimopoulou3, Charalampos Roussis1,2, Apostolos Aragmidanis3, Stylianos Orfanos1,5, 1Marianthi Simou Laboratory, 1st Dept. of Critical Care, Evangelismos Hospital, University of Athens Medical School, Athens, Greece; 21st Dept. of Critical Care, Attikon Hospital, University of Athens Medical School, Athens, Greece

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Conclusion: Our study indicate that PC gene rare mutations (c.1051C>G, c.1051C>A) may be associated with ALI/ARDS.
Results: Depending on the presence of haplotype-determining-point mutations, patients were divided into three haplotypes: H1 (n=59), H2 (n=17) and recombinant H1/H3 (n=16). ALI occurred in 53% of H2 carriers, 24% of H1 carriers and 50% of H3 carriers with odds ratios 1.0, 0.284 (Confidence Interval 0.090-0.904) and 0.963, respectively (p=0.033). Severe sepsis/septic shock was positively correlated with ALI/ARDS development, while APACHE II, SOFA, age and soluble EPCR levels were not independent predictors of ALI/ARDS.

Conclusion: EPCR genotype seems to be a determinant of ALI/ARDS development in critically ill patients. H1 haplotype carriers have a reduced risk of ALI/ARDS, as compared to H2 haplotype and H1/H3 carriers.

1686 Diagnostic value of Von Willebrand factor (VWF) in patients suffering from respiratory distress

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Introduction: Acute respiratory distress syndrome (ARDS) is characterized by an extensive alveolar capillary leak. Von Willebrand Factor antigen (VWF) is a macromolecular antigen that is considered as a marker of endothelial activation.

Aim: To investigate the diagnostic value of VWF antigen in patients with ALI/ARDS caused by poisoning or non-poisoning etiology.

Patients and methods: VWF antigen was measured in 52 patients with ALI/ARDS, 13 poisoned patients without ALI/ARDS and 20 control subjects.

Results: There was a highly significant difference between VWF level in patients and control groups (P ≤ 0.001). VWF level had a significant negative correlation with the ratio between PaO₂/FIO₂ in patients with respiratory distress. There was a non significant difference in VWF level between poisoned and non-poisoned cases. There was a significant relationship between the level of VWF and the severity of poisoning in patients with respiratory distress. Among the poisoned patients, the highest level of VWF was in patients with anticholinesterase poisoning. The difference between VWF level in poisoned patients with ALI/ARDS and those without was highly significant. The level of VWF didn’t affect patients’ need for mechanical ventilation or their mortality. The cut –off value of VWF at 100% specificity and 20% sensitivity was 0.99 units, while the cut-off –off value of VWF at 100% specificity and 60% sensitivity was 1.87 units.

Conclusion: VWF has a diagnostic value for ALI/ARDS but it does not differentiate between poisoning or non-poisoning etiology, nor does it predict outcome of ARDS. VWF is significantly increased in patients with anticholinesterase poisoning.

1687 Stimulation of NOD1 induces RIP2, TAK1 and p38 MAPK dependent pro-inflammatory signalling in human lung microvascular endothelial cells


Gram-negative bacteria are an important cause of septic shock. NOD1 receptors recognize peptidoglycan in the bacterial cell wall and initiate pro-inflammatory responses. We have previously shown in rodents that stimulation of NOD1 induces vascular dysfunction in vitro and profound shock in vivo. In this study we investigate the role of NOD1 in human lung microvascular endothelial cells (HMVEC) which represent a site of key importance in the pathophysiology of sepsis and acute lung injury.

HMVEC from healthy donors were cultured in 96-well plates. Cells were treated for 24 hours with vehicle ± LPS (TLR4) or iE-DAP (NOD1). In additional experiments cells were pre-treated for 1 hour with specific signalling inhibitors prior to addition of agonists (n=4–5). Cell activation was assessed by multiplex ELISA and by specific ELISAs for CXCL8 and 6-keto Prostaglandin F1α.

iE-DAP induced significant release of CXCL8, 6-Keto Prostaglandin F1α, IL-1β, IL-2, and IFNγ. SZ-7-oxo-zeazemon or BIRB0706 similarly inhibited responses to iE-DAP (Figure 1) or LPS (P<0.05;two-way ANOVA). By contrast, PP2 was more potent an inhibitor of iE-DAP (Figure 1) than LPS (P<0.05; two-way ANOVA).

In conclusion NOD1 is active in human microvascular endothelium and converges with TLR4 signalling at the level of TAK1 and p38 MAPK. NOD1 thus represents a potential target in the treatment of gram-negative sepsis.

1688 Lactate, pH and angiogenetic markers in exhaled breath condensate correlate with outcome and disease severity in patients with acute lung injury

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Acute lung injury (ALI) is characterized by increased capillary permeability, interstitial and alveolar oedema, influx of circulating inflammatory cells, and formation of hyaline membranes. Vascular endothelial growth factor (VEGF) has been correlated to a favourable prognosis in ARDS in a number of investigations. VEGF plays a role in regulating vascular permeability to water and protein.

The aim of this investigation was to characterize the role of VEGF, Angiogenin, basic fibroblast growth factor (bFGF), IL-8, and TNF-α in exhaled breath condensate (EBC) in mechanically ventilated patients with acute lung injury.

For this purpose, exhaled breath condensate was collected from 30 patients with ALI at 24 to 72 hours from start of mechanical ventilation and correlated with ventilatory parameters, clinical scores, and outcome. Cytokines were measured by a cytometric bead array (CBA). We observed a significant lower value of VEGF in EBC in the group with lower outcome compared to survival group (median:32.4 pg/ml vs. 108 pg/ml in survivors; Mann-Whitney test: p<0.0001) but no significant difference for Angio- genin, bFGF, IL-8, or TNF-α. In addition EBC-lactate and EBC-pH correlated positively with lung injury severity indices. There was a further correlation of bFGF and IL-8 in EBC with lung injury severity indices.

We conclude that measurement of lactate, pH, bFGF, and VEGF in EBC may provide information on prognosis in ALI.

1689 Which is the best source of mesenchymal cells to treat acute lung injury?

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Mesenchymal stem cells (MSC) may derive from bone marrow, adipose tissue or lung. Previous studies have shown that bone marrow derived mesenchymal stem cells (BM-MSC) exert beneficial effects in acute lung injury (ALI), but the effects of adipose tissue and lung derived mesenchymal cells (AD-MSC and L-MSC, respectively) have not been evaluated so far. The aim of this study was to investigate the effects of BM-MSC, AD-MSC, L-MSC on lung mechanics and morphometry, as well as inflammation and remodeling in an experimental model of ALI Forty-eight female Wistar rats (200-250g) received Escherichia coli lipopolysaccharide (LPS) intratracheally (100 μg/ALI) or saline (C). At 48 hours, ALI and C groups were further randomized into subgroups receiving saline (0.05 mL), BM-MSC, AD-MSC, and L-MSC (1 x 10^5) intravenously. Bone marrow cells were extracted from four male Wistar rats. The induction of differentiation showed that cells from bone marrow, adipose tissue and lung were able to generate osteocytes, adipocytes and chondrocytes besides presenting CD34+, CD90+ and CD29+ profile. At day 7, mesenchymal cells promoted a reduction in lung static elastance, resistive and viscoelastic pressures, alveolar collapse, collagen fiber content and number of neutrophils in lung tissue, independent of the source. However, the beneficial effects of BM-MSC and AD-MSC on lung parenchyma remodeling were greater than those observed with L-MSC. In conclusion, in the present LPS-induced ALI model, BM-MSC and AD-MSC therapies were more effective than L-MSC at modulating inflammatory and fibrogenic processes.

Supported by: CAPES, PRONEX, FAPERJ, CNPq

1690 Mesenchymal stem cells prevent early inflammation in a rat model of ventilator induced lung injury

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Background: Recent studies have suggested that bone marrow-derived mesenchy-
mal stem cells (MSC) might have potential therapeutic effects in acute lung injury (ALI), specifically in bleomycin-induced and bacterial LPS-induced lung injury models. However, whether MSC could induce an early anti-inflammatory response in lung injury induced by overventilation remains to be elucidated.

**Aim:** To assess the potential role of MSC in preventing or modulating early inflammation in healthy rats subjected to ventilator induced lung injury (VILI).

**Methods:** Adult male Sprague-Dawley rats (250-300 g) were anaesthetised, tracheotomised, intubated and paralyzed by intravenous instillation of pancuronium bromide. Nine rats were ventilated with a high tidal volume of 25 ml/kg (VILI) for 3 h. Five million of MSC were intravenously injected to 4 of these rats 30 min before starting ventilation. Spontaneously breathing anaesthetised rats (N=4) served as controls. After 3 h of VILI the animals were sacrificed and bronchoalveolar lavage inflammatory cells were assessed.

**Results:** In VILI, MSC significantly (p<0.01) decreased total neutrophil counts from 7620±3710 to 1580±470 (cells/μL), which was close to control values (787±344; p=0.6).

**Conclusion:** This preliminary result suggests that infusion of bone marrow-derived MSC prevents early inflammation in VILI.

Funding: L. Chimienti was a recipient of a RFS/Marie Curie Postdoctoral Research Fellowships 2010

215. Clinical application of exhaled biomarkers

2162 Exhaled molecular patterns change after experimental rhinovirus 16 infection in asthma

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**Rationale:** The majority of asthma exacerbations is caused by rhinovirus (RV) infection. Metabolomic assessment of exhaled Volatile Organic Compounds (VOCs) using an electronic nose (eNose) offers the opportunity to simplify and improve monitoring of asthmatics with exacerbations.

**Hypothesis:** We hypothesized that exhaled VOC-patterns change after experimental rhinovirus infection.

**Methods:** Patients with mild intermittent asthma (no ICS, age 22±3; M/F 4/5) and healthy controls (22±3; I/13) underwent intranasal RV16 inoculation. Efficacy of inoculation was assessed by antibodies and PCR. Exhaled breath was collected using a standardized method 1 day before (visit 1), and 4 days (visit 2) and 2 months (visit 3) after exposure. Exhaled VOCs were measured by eNose (Cyranose 320) resulting in breathprints. Changes in breathprints were analyzed by principal component and mixed model analysis.

**Results:** 9/14 Asthmatics/healthy controls were included. Breathprint principal components (PC) changed significantly in asthmatics between visits 1 and 2 (p<0.01), and between visits 1 and 3 (p<0.015), but there was no change between visits 2 and 3. Breathprints of healthy controls did not change between any visit.

**Conclusion:** Rhinovirus infection changes exhaled VOC-patterns in asthmatics and not in healthy controls. This suggests that the change in exhaled VOC-pattern during and after RV infection in asthma may be used to monitor and predict exacerbations.

1693 Increased exhaled breath condensate cysteinyl leukotriene concentration in exercise-induced bronchoconstriction

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**Background:** Several studies support the role of cysteinyl leukotrienes (Cys-LTs) in exercise-induced bronchoconstriction (EIB), however the concentration of these mediators during the development of EIB has not been investigated yet.

**Aim:** To study the effect of exercise on airway concentration of Cys-LTs in asthmatic patients by measuring Cy-LT in exhaled breath condensate (EBC).

**Methods:** Seventeen asthmatic patients with previous history of EIB and six healthy subjects participated in the study. Lung function was measured and EBC was collected at rest (baseline), immediately and ten minutes after exercise challenge on treadmill. Exhaled NO (FENO) was also determined at baseline. To compare the exercise-induced changes in FV1 and Cys-LT between groups, repeated-measures ANOVA was used. Pearson correlation was applied to assess the relationship between variables. Cys-LT levels are expressed as median (range).

**Results:** Baseline Cys-LT level was higher in asthmatic than in healthy subjects (168 pg/ml (112-223) vs. 77 pg/ml (36-119), p<0.03). Exhaled breath condensate Cy-LT concentrations in all asthmatic patients post-exercise (p=0.03), with the increase significantly greater in patients developing exercise-induced bronchospasm (n=7, p<0.03), while no change was observed in healthy controls (n=10, p=0.59). There was a strong correlation between baseline FENO and the maximal increase in Cys-LT concentration in the asthmatic group (r=0.01, r=0.57). A significant relationship was observed between the increase in EBC Cy-LTs and the exercise-induced fall in FV1.

**Conclusion:** Our study supports the concept that the release of Cys-LTs is involved in the development of EIB.

1694 Exhaled nitric oxide may predict future benefit in patients with poorly controlled asthma

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**Rationale:** Dynamic changes in exhaled nitric oxide fraction (FeNO) are highly predictive for asthma control, whereas its absolute values are often in discrepancy with patients’ clinical status.

**Aim:** To evaluate the potential of baseline FeNO to identify in regular clinical practice the individuals with suboptimal controlled asthma who have the potential to achieve control according to a guidelines-based approach.

**Methods:** 165 patients seen for two consecutive visits with uncontrolled asthma (defined as a score of ≤ 19 in the Asthma Control Test) at the first visit were included in the study. The exclusion criteria were limited to smokers and overlapping COPD since the study was purported to reflect the real-life practice.

**Results:** In ROC curve analysis, a greater absolute value of FeNO at the first visit
was associated with the acquirement of asthma control in the second one (AUC – area under the curve was 0.7816, p<0.0001). Its predictive performance with respect to the future control of the disease did not significantly differ between patients with and without allergic rhinitis (AUC was 0.7661 vs 0.7918; p = 0.35), even if the mean value of FeNO was greater in the former group (33.72±1.98 vs 29.27±1.96, p<0.0006). In uncontaminated asthma, values of FeNO > 35 ppb in patients with, and > 30 ppb in patients without allergic rhinitis, predicted future benefits (the positive predictive value was 85.42% and 91.97%, respectively).

Conclusion: Our results suggest that the fractional concentration of exhaled nitric oxide more strongly relates to asthma control and future benefit over time even in patients with underlying atopy, as expressed by the presence of allergic rhinitis.

1695 Exhaled nitric oxide is better related to bronchial responsiveness and eosinophil activation in children than adults with asthma

Andrei Malinovschi1, Christer Janson2, Pia Kalm-Stephens3, Kjell Alving3 .

Methods: The fraction of exhaled nitric oxide (FeNO), a marker of steroid-sensitive airways inflammation, is moderately related to bronchial responsiveness (BR) in asthma. Serum eosinophil cationic protein (sECP), a systemic eosinophil activation marker, is weakly-related to exhaled NO. However, no studies have concomitantly compared these relationships in children and adults with asthma.

Aim: To analyze in an ongoing asthma study the relation between exhaled NO and BR as well as sECP with respect to age of subjects.

Methods: FeNO, lung function, methacholine provocation (PC20FEV1), sECP measurements and allergy testing were performed in 208 patients with asthma (94 children aged 10-17 years and 114 adults aged 18-53 years) within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS).

Results: No differences between children and adults were found with regard to allergic sensitization (80% vs 84% atopic), lung function (FEV1, FV (Spred)) 90% (81, 99%) vs 93% (86, 103%) and asthma control (ACT score 21 (19, 23) vs 21 (19, 23) (all p-values >0.05). The correlation coefficients between FeNO and PC20 were rho=0.46, p<0.01 in children and rho=0.21, p<0.01 in adults. Similarly, FeNO was stronger related to sECP in children (rho=0.49, p<0.001) than adults (rho=0.25, p=0.006).

Conclusion: The relation between exhaled NO and bronchial responsiveness appears to be weaker in adults and this might be explained by other factors than ongoing allergic inflammation causing bronchial hyperresponsiveness, for example airway remodeling. The weaker relation between exhaled NO and sECP in adults warrants further research.

1696 Non-invasive biomarkers applied in a case-control study

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Background: Exhaled breath contains various potential noninvasive biomarkers for airway disease.

Aim: This study aims to evaluate the performance of known exhaled markers and to search for potential new markers in exhaled breath.

Methods: Asthmatic (N=72) and healthy (N= 67) children (6-12 years) donated exhaled breath condensate (EBC;RTube) and exhaled gasses (Tedlar bag). Fractional exhaled nitric oxide (FeNO) was measured (NIOX MINO). EBC pH was measured directly after sampling without deaeration. EBC 8- isoprostane was measured with an electronic nose.

Results: Increased FeNO values were observed in the asthmatic group compared to the healthy controls (Mann-Whitney U test; p=0.057), and in the allergic asthmatic patients compared to the non-allergic asthmatic patients (p=0.01). EBC pH was significantly lower in the asthmatic group compared to healthy controls (p=0.047). EBC 8-isoprostane was comparable between children with asthma and healthy controls, but was significantly increased in allergic asthma patients compared to non-allergic patients (p=0.032). Various proteins that might be relevant in respiratory health outcomes were for the first time identified in EBC, amongst which annexin A1 and A2, eukaryol A and B, cathepsin, gelsolin, and prolactin-induced protein.

Prediction models of selected proteolytic peptides or gasses were build (Support Vector Machine analysis) based on the health outcome asthma.

Conclusion: Exhaled molecules are influenced by asthma or allergy status. This study identified new exhaled molecules that might be relevant for respiratory health.

1697 Pattern of exhaled volatile organic compounds is altered in children with obstructive sleep apnea

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Background: Obstructive sleep apnea syndrome (OSAS) is a common disorder in children. Systemic and local airway inflammation is involved in its disease pathogenesis. Non-invasive tools for inflammation are needed in pediatricians. The analysis of exhaled volatile organic compounds (VOCs) by sensor arrays such as electronic noses offers a novel method to assess inflammation-related metabolic changes and oxidative stress.

Objective: To study if exhaled VOC pattern in children with OSAS can be discriminated with an electronic nose.

Methods: Eight children with mild to moderate OSAS (age 2±2 yrs) and ten healthy control subjects (10±3 yrs) were recruited. Subjects did not present any acute or chronic airway disease. After a single deep inspiratory capacity, VOC pattern of exhaled breath (collected from the lower airways without the dead space) was recorded with Cyanose 320 (Smiths Detection) and analyzed off-line using principal component analysis, Mahalanobis regression and receiving operator curve (ROC) analysis (SPSS 16.0).

Results: All subjects provided technically adequate breath samples. Exhaled VOC pattern of OSAS patients could be discriminated from that of control subjects using the Mahalanobis method (Wilks’ lambda=0.02; 73% classification accuracy) and also with ROC analysis (sensitivity: 88%; specificity: 70%; positive predictive value: 70%; negative predictive value: 88%).

Conclusions: In this first preliminary study, we show that exhaled VOC sampling is feasible in children, and VOC pattern analysis can discriminate patients with OSAS from healthy controls. Exhaled VOC analysis might serve as a new tool for airway inflammation in children.

This study was supported by OTKA 68808.

1698 Increased exhaled nitric oxide predicts new-onset rhinitis in asymptomatic children

Andrei Malinovschi1, Christer Janson2, Pia Kalm-Stephens3, Kjell Alving3 .

Methods: A total of 959 randomly selected schoolchildren, aged 13-14 years, answered questions on respiratory and allergy symptoms, family history of asthma, lung function and FeNO were also measured at baseline. A follow-up with the same test battery is planned four years later. After exclusion of subjects with asthma or rhinitis symptoms at baseline, 555 participants were eligible for the present study.

Results: Subjects with new-onset rhinitis (n=92) had a trend of higher FeNO than subjects who did not develop rhinitis (p=0.06). Increased FeNO predicted new-onset rhinitis in a multiple logistic regression model (p=0.009) and the risk of new-onset rhinitis was 2.4-fold (1.2, 4.4) elevated if FeNO > 90th percentile of all included subjects (n=555). A similar risk increase for new-onset rhinitis, 2.4 (1.2, 4.9) was found in subjects with no allergy symptoms and 2.3 (1.04, 5.1) after further excluding subjects with a family history of asthma.

Conclusion: Increased FeNO levels predicted new-onset rhinitis in this population-based study of schoolchildren. The predictive value in subjects without allergic symptoms or family history of asthma suggests that these children with increased FeNO should be tested for allergy and followed-up.

1699 Differentiation of chronic obstructive pulmonary disease (COPD) including lung cancer from healthy control group by breath analysis using ion mobility spectrometry

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Introduction: Non-invasive methods with potential for diagnosis of lung diseases and increasing interest: Ion mobility Spectrometry detects volatile analytes within human breath directly. Therefore its usefulness in discriminating COPD patients and healthy persons is tested.

Methods: Exhaled breath of 132 persons (97 COPD patients [35 without lung cancer, 62 with lung cancer] and 35 healthy volunteers) was investigated using an Ion Mobility Spectrometer (IMS) coupled to a Multi-Capillary Column (MCC)
216. Molecular pathology and functional genomics of lung disease

1760 Late-breaking abstract: The TERT-CLPTM1L locus for lung cancer predisposes to bronchial obstruction and emphysema

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Clinical studies suggest that bronchial obstruction and emphysema increase susceptibility to lung cancer. We assess the possibility of a common genetic origin and testability of the lung cancer susceptibility locus on chromosome 5p15.33. In 3074 individuals the rs11568834 T>G variant was genotyped. The presence of the T allele was associated with increased odds of requiring GINA step 4 treatment: heterozygosity was associated with 1.56 (1.18-2.06) times the risk of requiring treatment (OR=1.72; CI=1.29-2.29; P=0.000); the frequency of the T allele was 14.7% in controls and 19% in patients (P=0.004). Accounting for rs11568834, the presence of the T allele was associated with increased odds of requiring GINA step 4 treatment: heterozygosity was associated with 1.70 (1.31-2.21) times the risk of requiring treatment (OR=1.86; CI=1.46-2.37; P=0.000).

1761 Late-breaking abstract: Possible association between vitamin D receptor SNP FokI and treatment response in asthmatic children

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Introduction: An association between poor asthma control and low 25OH Vitamin D (25OHD) has been shown. Single nucleotide polymorphisms (SNP) in the gene encoding 25OHD receptor (VDR) have been associated with asthma. Hypothesis: asthma control is associated with 25OHD levels and VDR SNP.

Methods: Total 25OHD values in healthy children were obtained from a sample of a previous study. Asthmatics treated with at least 3 months of inhaled steroids were enrolled in outpatient clinics. A clinical questionnaires of asthma severity was applied and blood was drawn. 25OHD levels were measured with Radioimmunounassay and SNP were analyzed by a standard PCR-RFLP assay.

Results: 75 asthmatic children (9.6±2.5 yrs) and 226 healthy children (10.2±4.8 yrs), were studied. 25OHD levels were 23.9±10.7 and 22.2±7.6 ng/ml respectively (p=0.122). No significant differences were found between controlled and uncontrolled asthmatics (24.9±6.1 and 21.5±7.3 ng/ml respectively). Analysis of FokI (rs10735810) SNP revealed that all patients (16/16) requiring GINA step 4 treatment were heterozygous for the C allele. The presence of the C allele was less frequent in patients in step 2 (30/33) and 3 (16/24) vs patients in step 1 (p=0.007). No significant differences in the other SNP (rs731236) and no association of neither SNP with asthma control status, were found.

Conclusions: This pilot study established a possible association between FokI C allele and need of higher steroid doses for asthma control. VDR might play a role in asthma treatment response. Further research is required to validate it.

1702 TNF-derived TIP peptide reduces lung dysfunction in experimental influenza A virus infection

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Background: Permeability edema during Influenza A virus (IAV) infection is characterized by reduced alveolar liquid clearance (ALC) and pulmonary endothelial hyperpermeability. Mortality after IAV infection is mainly due to secondary pneumococcal infections and occurs after antibiotic therapy, which can release the toxin pneumolysin (PLY) in the lungs.

Aims: To investigate whether the TNF-derived TIP peptide, which reduces PLY-induced edema, can blunt IAV-induced ALC dysfunction and combined IAV/PLY-induced barrier dysfunction.

Methods: ALC is assessed in BALB/C mice infected i.n. for 2d with 10,000 FFU/mouse (strain H1N1-AWSN/33), using the BSA dilution method. We measure IAV/PLY-induced changes using a modified ELISA (Wien Janssens1). We applied and blood was drawn. 25OHD levels were measured with Radioimmunounassay in serum samples of asthmatics, 2 SNP in the VDR gene.

Results: A single analyte could be identified, that allowed a separation of the ALC phenotype. Discriminant analysis was applied to find discriminant analytes.

In BALB/C mice exposed to IAV/PLY, the peak was characterized as cyclohexane (CAS 108-94-1). The sensitivity obtained was 60%, the specificity 91%, the positive predictive value 95%. The peak was characterized as cyclohexanone (CAS 108-94-1). The presence of the C allele was associated with increased odds of requiring GINA step 4 treatment: heterozygosity was associated with 1.56 (1.18-2.06) times the risk of requiring treatment (OR=1.72; CI=1.29-2.29; P=0.000); the frequency of the T allele was 14.7% in controls and 19% in patients (P=0.004). Accounting for rs11568834, the presence of the T allele was associated with increased odds of requiring GINA step 4 treatment: heterozygosity was associated with 1.70 (1.31-2.21) times the risk of requiring treatment (OR=1.86; CI=1.46-2.37; P=0.000).

Conclusions: The TIP peptide represents a therapeutic candidate for the treatment of IAV-associated lung dysfunction, since it interferes with both IAV infection-associated ALC and barrier dysfunction, upon reducing PKC-a activation.

1703 Oxidative stress during high altitude expedition and its influence on vessel tone-modifying mediators

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Introduction: Hypoxia-induced excessive pulmonary vasconstriction is assumed to be the main cause of life-threatening high altitude pulmonary edema. Decrease of nitric oxide (NO), a potent vasodilator, has been suggested to play a significant role in hypoxia-induced vasconstriction. To study alterations of prolonged hypobaric hypoxia, serum samples were drawn from 34 healthy mountaineers up to 8685 m during a Swiss research expedition to mount Muztagh Ata (7549 m) in Western China. Comprehensive metabolomics analysis using a mass spectrometry-based targeted approach revealed a pronounced systemic oxidative stress during high altitude exposure. Detecting more than 390 parameters, a significant increase of lipid peroxidation was shown. Methionine sulfoxide, determined in relation to methionine, furthermore serves as a robust indicator of oxidative stress and showed highly increased values of 30% (mean at 550m), compared to values of 20% in septic patients. We also found relevant functional impairment of phenylalanine hydroxylase and nitric oxide synthase (NOS), enzymes which both require an oxidant-sensitive co-factor. Consequently, very low levels of NO were found. In addition, significant increase in the serum concentration of vessel tone modifiers such as leukotrienes and prostaglandins were found.

This novel and holistic approach extends the mechanistic understanding of hypoxia-related oxidative damage to a biochemical level and unravels underlying biochemical pathways involved in hypoxia-induced pulmonary vasoconstriction. Together, we demonstrate further insight into the molecular pathogenesis of hypoxia-related disorders.
1704 Systemic upregulation of neutrophil α-defensins and serine proteases in neutrophilic asthma

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Background: The well-characterised airway inflammatory phenotypes of asthma include eosinophilic, neutrophilic, mixed eosinophilic/neutrophilic and pauci-granulocytic asthma, defined by the proportion of sputum granulocytes. Systemic inflammation is now recognised as an important part of some airway diseases, but the role of systemic inflammation in the pathogenesis of asthma phenotypes remains unknown.

Methods: Induced sputum samples and peripheral blood were collected from participants with asthma (n=30). Airway inflammatory cell counts were performed on induced sputum and inflammatory phenotype assigned based on the airway eosinophil and neutrophil cut-offs of 3% and 61% respectively. Gene expression profiles were generated (Illumina Human-8 V3) from whole blood RNA and analysed using GeneSpring GX 11.

Results: There were 6 genes classified as differentially expressed between the 4 asthma phenotypes including the α-defensins (DEFA) 1, 1B, 3 and 4, neutrophil proteases cathepsin G (CTSG) and elastase (ELA2). Significant expression of DEFA1, 1B, 3, 4, CTSG and ELA2 was significantly higher in the neutrophilic asthma phenotype. Microarray results were successfully validated using real-time PCR. Plasma elastase was significantly elevated in people with neutrophilic airway inflammation.

Conclusion: There is systemic upregulation of α-defensin and neutrophil protease expression in neutrophilic asthma, which may reflect the pro-inflammatory effects on the bone marrow and the release of immature neutrophils into the circulation. This demonstrates a systemic inflammatory component in neutrophilic asthma that further differentiates this from other asthma phenotypes, and indicates different mechanisms.

1705 Dysregulated miRNAs and their predicted mRNA targets in emphysema lungs

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There is increasing recognition of the importance of microRNAs (miRNAs) as short non-coding RNAs that post transcriptionally regulate gene expression. Identification of the role of miRNAs in COPD would help better understanding of disease pathogenesis and use as biomarkers for diagnostic purposes or therapeutic targets. Our aims were i) to identify miRNAs dysregulated in mild and moderate emphysema, and ii) to identify mRNAs regulated by miR-34c-5p in BEAS-2B and HFL cell lines.

Methods: i) miRNA microarray profiling (Agilent Human miRNA profiler G4470A) was performed on 29 non-tumour lung tissues obtained from The Prince Charles Hospital tissue bank. Patients were classified as mild (n=9) and moderate (n=20) emphysema according to lung function measurements (KCO and FEV1). Technical validation was performed on the selected miRNAs using quantitative real-time PCR. ii) Genomic mRNA expression changes from transient transfection of miR-34c-5p (candidate miRNA in BEAS-2B and HFL cells) were measured using Illumina HumanHT-12 V3 arrays.

Results: COPD patients had mean (SD) age 68 (6) years, FEV1: 72 (17%) predicted and KCO 70 (10%) predicted. Five miRNAs were identified (p<0.01) as differentially expressed in non-tumour lung tissues in mild vs moderate emphysema patients. Upregulation of miR-34c-5p in respiratory cell lines down-regulated predicted mRNAs.

Conclusions: We have shown that miRNAs are associated with COPD severity and modulate expression of their predicted mRNAs. Support: NHMRC Biomedical Scholarship (SF), NHMRC Career Development Award (JY), The Prince Charles Hospital Foundation, Australian Lung Foundation/Boehringer Ingelheim COPD Research Fellowship.

1706 Differentiation between squamous cell carcinoma (SCC) and adenocarcinoma (AC): Expression of immunohistochemical (IHC) markers in a tissue microarray (TMA) of >1000 NSCLC cases

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Introduction: Distinguishing SCC from AC has become crucial for tailored therapies of NSCLC. Many patients are inoperable at the time of diagnosis of NSCLC, >65% of the diagnoses are performed in small biopsies (Bx). The “IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma” (Travis W.D., Brambilla E. et al. JTO 2011; 6:244-85) firstly includes diagnostics in Bx in addition to resection specimen. We investigated the expression of IHC markers in a TMA studying Bx.

Materials and methods: The IHC markers CK5/6, p63, desmocollin-3, CK7, TTF1, and napsin were investigated in a TMA from a primary cohort of 1005 patients with resected NSCLC.

Results: For SCC, desmocollin-3 showed the highest, CK5/6 a medium, and p63 the lowest specificity. The sensitivity of desmocollin-3 was similar to the sensitivity of CK5/6 and p63. Desmocollin-3 was expressed in about 85%, CK5/6 and p63 in >90% of all SCC.

For AC, TTF1 and napsin revealed a considerably higher specificity than CK7. The sensitivity of napsin did not exceed the combined sensitivity of CK7 and TTF1. CK7 was expressed in >95% of all AC, TTF1 in <90%, and Napsin in <80%.

Conclusions: To spare tissue for further (e.g. molecular) analyses, diagnostic algorithms for NSCLC Bx must be established. If histology alone cannot distinguish between SCC and AC, a combination of TTF1, napsin, CK5/6 and desmocollin-3 can serve as initial diagnostic marker panel. CK7 and p63 could be sequentially specific, if necessary, because of lower specificity. Currently a TMA of 300 further NSCLC is investigated, data from all 1300 NSCLC will be presented.

1707 DNA copy number alterations in squamous metastatic lesions predict lung cancer

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No biomarker can reliably predict cancer risk in individual subjects who present with AFB-visualized premalignant lesions. Our present study was set out to identify AFB-visualized squamous metastatic (SqM) lesions with malignant potential by DNA copy number profiling.

Within our cohort of 474 subjects at risk of lung cancer who underwent regular AFB examinations, 6 (1.3%) subjects showed rapid progression from SqM to carcinoma (in situ) (cases). P53, p63 and KI-67 immunostaining patterns and arrayCGH-based DNA copy number profiles of progressive SqM lesions (n=6) were compared to those of a subset of SqM from lung cancer-free (controls; n=23). Specific DNA copy number alterations (CNAs) linked to cancer risk were identified and accuracy to predict cancer in this series was determined.

While clinicopathologic characteristics and immunostaining patterns were not related to clinical outcome of SqM, the mean number of CNAs in SqM of cases (23%, range 0.48-39%) was significantly higher compared to controls (0.09%, range 0.1-32%, p<0.01). Significantly more frequently altered in cases were 3p26.3-3p11.1, 3q26.2-2q9, 9p13-3p13.2, and 17p13.3-1p12 (FWER<0.10). In cases, baseline-detected CNAs persisted in subsequent biopsies taken from the initial site (median 93%, range 68-99%), and levels increased towards cancer progression (p=0.028). CNAs at 3p26.3-3p11.1, 3q26.2-2q9, and 6q23.3-2q3.3 predicted endobronchial cancer risk for AFB-visualized SqM with 97% accuracy.

Our data strongly suggest that CNAs predict endobronchial cancer in individual subjects diagnosed with AFB-visualized SqM, and may be used to guide intervention to prevent lung cancer.

217. Cardio-pulmonary interactions

1708 Late-breaking abstract: The diaphragm and abdominal muscles act on the abdomen to displace blood to the extremities during exercise

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We have recently demonstrated (Aliverti et al. J Appl Physiol, 2010) that during quiet breathing the diaphragm serves the double function to ventilate the lung and to shift blood from the splanchnic to the peripheral vascular bed to the extremities. We hypothesized that with simultaneous contraction of abdominal muscles, such as occurs during exercise, the circulatory function of the diaphragm can be considerably enhanced. Six healthy subject performed a submaximal constant exercise workload test (repeated foot flexion at ~60% of max workload) within a whole body plethysmography (WBP) measuring changes in body volume (Vb). Simultaneously, changes in volume of the trunk (Vt) were measured by orthopneic plethysmography. Blood shifts between trunk and extremities (Vb), were determined...
as dVtr-dVb. In all subjects, intra-breath variations of Vbs were bimodal. Vbs initially decreased and then increased during inspiration; Vbs then decreased in the first part of expiration, and increased again in the second part. After 1 min of exercise, within-breath tidal Vbs increased by 175±122 ml (p<0.018) from rest, the blood accumulated into the extremities was 304±338 ml (p<0.05) and abdominal volume at end-expiration decreased by 0.50±0.32 L (p=0.012).

We conclude that a precise control mechanism of the diaphragm and abdominal muscles determines intra-breath variations of Vbs during exercise. Due to the high frequency of tidal Vbs there is not adequate time for a complete refilling of the splanchnic blood reservoir at each abdominal compression, and this results into a significant shift of blood from the trunk to the extremities during exercise. When needed, this should be clinically useful.

### 1709
**Right ventricular contractility at rest and during exercise in COPD**

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**Rationale:** COPD patients show a limited stroke volume response to exercise. This is thought to be due to an increased right ventricular (RV) afterload. Whether an impairment to increase RV contractility contributes to the impaired stroke volume response is unknown. Therefore, the aim of this study is to determine whether RV contractility changes during exercise in COPD patients.

**Methods:** Nine patients with COPD (GOLD II-IV) underwent right heart catheterisation and subsequently cardiac MRI at rest and during submaximal exercise. With cardiac MRI RV volumes were measured. During right heart catheterisation RV pressure curves were continuously measured. As a measure of contractility, the maximum rate of rise of RV pressure (dP/dtmax) was obtained from an averaged RV pressure waveform over several respiratory cycles. Then, dP/dtmax was normalized for RV end-diastolic volume, i.e. dP/dtmax/EDV (1).

**Results:** In all patients dP/dtmax/EDV increased with exercise. At rest mean dP/dtmax/EDV was 3.6±1.3 mmHg/s/ml, while during exercise it was 6.5±3.7 mmHg/s/ml (p<0.001). RV end-systolic volume did not change with exercise.

**Conclusions:** COPD patients show an increase in RV contractility. The increase in contractility does not result in a decrease in RV end-systolic volume.

**Reference:**

### 1710
**Right ventricular output in chronic obstructive pulmonary disease during expiration is impaired by reduced venous return**

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**Background:** High positive airway pressure impedes venous return and right ventricular (RV) output in mechanically ventilated patients. Whether this is also the case in normally breathing COPD patients, where the expiratory intrathoracic pressure is increased due to airway obstruction, is unknown. We investigated the effects of intrathoracic pressure on venous return and how this perturbs RV output during expiration at rest and during exercise.

**Methods:** Sixteen COPD-patients (GOLD II-IV) underwent simultaneous measurements of intrathoracic, right atrial (RA) and pulmonary artery pressures at rest and during exercise. Intrathoracic and RA pressure were used to calculate RA filling pressure. Dynamic changes in pulmonary artery pulse pressure during expiration were examined to evaluate changes in RV output.

**Results:** Pulmonary artery pulse pressure decreased up to 40% during expiration (figure 1). This decline was associated with a low RA filling pressure (r= 0.64). During exercise, a similar decline in pulmonary artery pressure was observed. Intra-thoracic pressure and RA pressure increased similarly, resulting in an unchanged RA filling pressure.

**Conclusions:** We show that in COPD, pulmonary artery pulse pressure declines during expiration; most prominent in patients with a low RA filling pressure. This implies that spontaneous breathing already impairs venous return and by that RV output in COPD.

### 1711
**Effects of hyperoxia and helium-hyperoxia on the cardiocirculatory responses to incremental exercise in hypoxemic patients with COPD**

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Heliox breathing might positively impact upon the haemodynamic responses to exercise in non-hypoxemic patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) (Chiappa, GR et al. Am J Respir Crit Care Med, 179:1004, 2009). There is, however, a lack of evidence of whether these beneficial effects would also be found in patients with more advanced cardiovascular impairment, i.e., hypoxemic, GOLD stage IV patients. On a double-blind study, 13 patients (FEV1= 35.4±9.1% pred; PaO2= 57.7±7.0 mmHg) were submitted to maximum incremental cardiopulmonary exercise tests while breathing hyperoxia (H2O2= 40% O2) or helium-hyperoxia (He-HiOX= 60% He/40% O2). Stroke volume (SV, ml) and cardiac output (CO, L/min) were non-invasively monitored by impedance cardiography (PhysioFlow® Manatec Inc, France). Peak work rate (WR) was improved with He-HiOX compared to HiOX (52±21 W vs. 46±18 W); in addition, end-expiratory lung volume (EELV) was slightly, albeit significantly, reduced (5.50±1.25 vs 5.61±1.30 L; p<0.05). At iso-WR, He-HiOX was associated with higher SV and CO than HiOX (92±8 ml vs. 84±2 ml and 6.9±1.3 L/min vs. 8.7±1.9 L/min, p<0.05). Improvement in CO with He-HiOX was negatively related to resting EELV (r=-0.72, p=0.01) but not with baseline CO and PaO2 (p>0.05). In conclusion, hyperoxic heliox enhances the cardiocirculatory responses to exercise compared to hyperoxia alone in less hypoxinilated patients with advanced, hypoxemic COPD. These data indicate that increased operational lung volumes are related to deleterious haemodynamic effects in this patient sub-population.

### 1712
**Predictors of improvement in peak exercise capacity with helium-hyperoxia in severely-impaired COPD patients under long-term oxygen therapy**

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Heliox can improve exercise tolerance in ventilatory-limited patients with chronic obstructive pulmonary disease (COPD). Unfortunately, however, these benefits are quite heterogeneous in patients with similar levels of resting airflow obstruction. In order to gain further insight into the determinants of such variability in hypoxemic patients with advanced COPD, we evaluated 24 males (GOLD stage IV) who were under long-term O2 therapy. Patients underwent maximum incremental cardiopulmonary exercise tests while breathing hyperoxia (H2O2= 40% O2) or helium-hyperoxia (He-HiOX= 60% He/40% O2). Peak work rate (WR) was significantly improved with He-HiOX compared to HiOX (54±26 W vs. 48±23 W). This was associated with increased mean ins and expiratory flows and
larger tidal volumes; in addition, end-expiratory lung volume was lower at peak exercise (5.5±1.2 L vs 5.6±1.3 L; p<0.05). Δ[He-HbO2–Hb] WR was positively related to markers of lung hyperinflation including total lung capacity and residual volume (r=0.52 and r=0.46; p<0.05). Interestingly, however, fat-free mass (FFM) also showed to be strongly related to ΔWR; in fact, FFM was the only independent predictor of ΔWR on a multiple regression analysis (r²=0.66; p<0.001). We conclude that once patients with advanced COPD are relieved from the “central” ventilatory constraints by breathing hyperoxic heliox, appendicular muscle mass becomes an important determinant of maximal exercise capacity. The above data lend support to the notion that preserved muscle mass is important for improved respiratory mechanics be translated into enhanced peak exercise capacity in these patients.

1713 Tissue deoxygenation kinetics induced by acute hypoxic exposure at rest in humans
Samuel Verges1, Thomas Rupp1, Marc Jebou2, Guillaume Milet2, Thomas Lety3, Véronique Bricourt1, Bernard Wuyam4, Stéphane Perrey5,1. HP2 Laboratory (U1042), UP Recherche sur l’Exercice, Hôpital Sud, INSERM, Joseph Fourier University, University Hospital, Grenoble, France; 2Exercise Physiology Laboratory, Jean Monnet University, University Hospital, St. Etienne, France; 3Movement to Health (M2H), Montpellier University, Euromed, Montpellier, France.

The impact of hypoxia on tissue oxygenation per se involves complex mechanisms. How muscle and brain face the hypoxic stress over several hours of hypoxic exposure (HE) remain unknown. Therefore, this study aimed to investigate the effects of 4-hours HE at rest on muscle and cerebral (de)oxy-hemoglobin kinetics. Twelve healthy males seated quietly while breathing the appropriate gas mixtures. After 10-min of normoxia (P[O2]=0.21), subjects were exposed for 4-h to hypoxia (HE, P[O2]=0.12) or normoxia (control condition), and then again for normoxia to 15 min. Muscle and cerebral oxygenation (NIRS), pulse oxygen saturation (SpO2) and heart rate variability were measured continuously. COPD are relevant from changes of oxy-(Δ[HbO2]), deoxy-(Δ[Hb]) and total-hemoglobin (Δ[HbTot]) were measured from baseline level.

SpO2, faSO2 and faHbO2 were at baseline level during the first 20 min of HE and then remained stable. In the same time, HE resulted in general sleep-hyposaeration. After a transient rise at 20 min of HE, muscle Δ[Hb] restored to baseline values whereas Δ[HbO2] and Δ[HbTot] were reduced from 120 to 240 min of HE only. Cerebral Δ[HbO2] rose markedly at 20 min of HE and remained constant until the end of HE. Cerebral Δ[Hb] was reduced over the first 120 min of HE but re-increased afterwards towards baseline values together with an increase in Δ[HbTot]. Muscle and brain both showed hyper-oxygenation status post HE. This study provided new insights on i) differential (de)oxy-hemoglobin kinetics in brain and muscle in response to sustained HE, ii) a biphasic cerebral tissue adaptation in the first 30 min, and iii) a tissue hyper-oxygenation after return to normoxia.

1714 Blood shift during cough in healthy subjects
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Double Body Plethysmography (DBP), which combines both total body plethysmography and opto-electronic Plethysmography, has been recently developed to measure the amount of blood displaced from the thorax to the extremities (Aliverti et al, J Appl Physiol, 2010). We hypothesized that also during cough a significant amount of blood can be displaced from the trunk to the extremities. We studied 7 healthy subjects (age: 28±6.2±5 yrs) during series of voluntary coughs at four different operating volumes: functional residual capacity (FRC), total lung capacity (TLC) and two intermediate volumes between FRC and TLC (namely, FRC+ and FRC++). BS from the thorax to the extremities were measured by DBP during quiet breathing and during cough at each operating lung volume. The results are shown in figure. BS during cough resulted significantly higher than during QB (p<0.001). BS increase with increasing operating volume, being maximal at total lung capacity (figure). These findings might help to better understand the cardiopulmonary interactions during cough and the mechanisms by which coughing during asthmatic cardiac arrest can maintain consciousness in human subjects.

218. Viral respiratory infections in children: causes and consequences

1716 Effect of inhaled hypertonic saline solution to treat infants hospitalized with viral bronchiolitis

Background and aims: At present only symptomatic treatment is available for acute viral bronchiolitis, none of these are evidence-based. Recent trials show a reduction in hospital stay after inhalation of 3% hypertonic saline solution. This randomised double-blind, placebo-controlled interventional multicenter trial, performed at 12 Dutch hospitals, compares nebulisation with hypertonic saline, either a 3% or 6%, with 0.9% isotonic saline. The primary end point is the time to discharge, aiming to achieve a 25% reduction in hospital stay. Methods: Children younger than two years with clinical diagnosis of viral bronchiolitis, not responding to a single inhalation with Salbutamol may be included. Children younger than two years with clinical diagnosis of viral bronchiolitis, not responding to a single inhalation with Salbutamol may be included. The primary end point is the time to discharge, aiming to achieve a 25% reduction in hospital stay. Methods: Children younger than two years with clinical diagnosis of viral bronchiolitis, not responding to a single inhalation with Salbutamol may be included. Children younger than two years with clinical diagnosis of viral bronchiolitis, not responding to a single inhalation with Salbutamol may be included. Children younger than two years with clinical diagnosis of viral bronchiolitis, not responding to a single inhalation with Salbutamol may be included. Conclusions: Preliminary analysis showed no significant reduction in hospital stay but a trend that 3% hypertonc saline is the most effective regarding duration of hospital stay, need for tube feeding and supplemental oxygen shows no significant difference, but there’s a trend that 3% seems to be more effective than the other 2 concentrations. Conclusions: Preliminary analysis showed no significant reduction in hospital stay but a trend that 3% hypertonc saline is the most effective regarding duration of hospital stay, need for tube feeding and supplemental oxygen shows no significant difference, but there’s a trend that 3% seems to be more effective than the other 2 concentrations.
hypertonic saline seems safe but has no additional benefit even compared with 0.9%. More research will be necessary to clear up this trend.

1717
7% hypertonic saline and hyaluronic acid and in the treatment of infants mild-moderate bronchiolitis
Raffaella Nenna, Stefano Papasso, Massimo Battaglia, Daniela De Angelis, Laura Petraca, Dani Felder, Serena Salvadori, Rosaria Berrardi, Micol Roberti, Paola Papadopoulou, Fabio Midulla. Department of Paediatrics, Sapienza University of Rome, Rome, Italy
The treatment of bronchiolitis is only supportive. The aim of our study was to evaluate the efficacy of hypertonic saline and hyaluronic acid (HS-HA) given by inhalation, in infants hospitalized for mild-moderate bronchiolitis. In a double-blind placebo-controlled study, 42 infants (26 males) less than 6 months of age (median age: 2.8 months) were enrolled and assigned to receive either HS-HA (7% NaCl + 0.1% HA) (n=21) or normal saline (n=20) at a dose of 2.5 ml twice a day for three days. To all infants a clinical severity score was assigned at the admission and four times daily during the hospitalization. Main outcome measures of our study were: number of days of hospitalization and reduction of the severity score. No differences were observed between the two groups for sex, age and clinical severity score at the admission. One child interrupted the protocol in the study group and two in the placebo group. 21% of children in the study group and 11% in the placebo group had mild cough after the aerosol. No difference was observed between the two groups with regard to the number of days of hospitalization (placebo group: 3.5 days vs study group: 3.1 days p=0.4) and to the clinical score reduction during the first three days of hospitalization (placebo group: 3.3 vs study group: 3.7 p=0.6). HS-HA is a safe but not effective therapy in treating infants hospitalized for mild-moderate bronchiolitis.

1718
Evaluating the risk of lower respiratory tract infection (LRTI) hospitalizations due to respiratory distress syndrome (RDS) in late preterm
Katharina Bueesch1, Hoa Hong1, Kathrine Gooch2. 1Global Health Economics and Outcomes Research, Abbott GmbH & Co. KG, Ludwigshafen, Germany; 2Global Health Economics and Outcomes Research, Abbott Laboratories, Chicago, United States
Background: Premature birth results in underdeveloped lung function that increases the risk for respiratory infection and morbidity. The prevalence of RDS requiring intervention in premature births is significant, including those considered late preterm. The aim of the study was to evaluate whether bronchiolitis hospitalizations in infants born late preterm is significant, including those considered late preterm. The aim of the study was to evaluate whether bronchiolitis hospitalizations in infants born late preterm are related to RDS. Methods: Late premature infants (33-36 weeks gestational age) hospitalized within the first year of life for a LRTI were extracted from the Medical Claims database (2000-2008). Univariate analyses were conducted to compare the differences between infants with and without an RDS event at birth. A multivariate model was developed to determine the independent association of RDS and LRTI hospitalization. Statistical significance was set at p=0.05.
Results: 31178 late preterm infants (52% male) were identified during the study timeline. 2297 (7.4%) late preterm infants were hospitalized due to a LRTI; a hyaline membrane disease or RDS diagnosis (ICD-9 code: 769) was observed in 962 late premies (3%). Multiple logistic regression analysis showed a strong and significant relationship between RDS and LRTI hospitalization (OR 5.2, 95% CI 4.4–6.2).
Conclusion: Late preterm infants with RDS event at birth are 5 times more likely to be hospitalized due to LRTI during the first year of life compared to late preterm without RDS event at birth. This risk factor should be considered when evaluating a premature infants risk for respiratory hospitalization.

1719
Rhinovirus lower respiratory tract infections and healthcare utilization of prematurely born infants during infancy
Simon Drysdale1, Mireia Alcazar1, Therese Wilson1, Simon Broun1, Gerard F. Rafferty2, Melvin Smith2. 1Department of Clinical Medicine, Imperial College London, London, United Kingdom; 2Global Health Economics and Outcomes Research, Abbott Laboratories, Chicago, United States
Aim: To determine if BAFF expression is elevated in the airways of infants with RSV lower respiratory tract infections (LRTIs) compared to infants born prematurely without RSV LRTI. Methods: Cultures of primary airway epithelial cells isolated from healthy children were infected with RSV A2 strain, and RV. Airway Epithelial cell expression of the B cell differentiation factor, B cell activating factor of the TNF family, BAFF was induced by RSV infection both in vivo and in vitro. To further confirm these results BAFF mRNA was measured by qPCR in bronchial brushings from patients with RSV bronchiolitis (n=5) and healthy infants (n=4). Average BAFF mRNA expression was around 20 fold higher in samples obtained from infected infants (p<0.01). In vitro cultures of primary airway epithelial cells isolated from healthy children were infected with RSV A2 strain, BAFF mRNA expression was induced 200 fold with maximum expression at 12 hours post infection (n=4, p<0.01). Protein analysis showed expression of up to 170pg BAFF protein at 48 hours post infection.

1720
Human respiratory syncytial virus infection in vivo and in vitro induces expression of the B cell differentiation factor BAFF
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Background: In RSV disease, innate immune mediators expressed by infected airway epithelial cells are known to strongly influence both early inflammatory responses and the subsequent development of an adaptive immune response. Human respiratory syncytial virus infection in vivo and in vitro induces BAFF expression. Aim: To determine if BAFF expression is elevated in the airways of infants with severe RSV Bronchiolitis and if RSV infection of primary Airway epithelial cells in vitro induces BAFF expression.
Methods: BAFF protein, as measured by ELISA, was increased in bronchiolar alveolar lavage fluid collected from the lungs of infants with severe RSV infection (n=10, mean 833pg/ml). Non infected control groups, admitted for elective surgery had lower levels (n=7, mean 12pg, p<0.027). To further confirm these results BAFF mRNA was measured by qPCR in bronchial brushings from patients with RSV bronchiolitis (n=5) and healthy infants (n=4). Average BAFF mRNA expression was around 20 fold higher in samples obtained from infected infants (p<0.01). In vitro cultures of primary airway epithelial cells isolated from healthy children were infected with RSV A2 strain. BAFF mRNA expression was induced 200 fold with maximum expression at 12 hours post infection (n=4, p<0.01). Protein analysis showed expression of up to 170pg BAFF protein at 48 hours post infection.

1721
Prenatal exposure to PCBs and dioxins is associated with increased risk of wheeze and infectious diseases in 2-year-old children
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Food may contain toxicants (from environmental pollution or formed during food preparation). These toxicants may cross the placentae barrier and affect the foetus immune system. The aim of this study was investigated if prenatal exposure to acrylamide, dioxins and polychlorinated biphenyls (PCBs) affect the children’s immunological health status. Pregnant women were recruited to the birth cohort Brøm (n=205). The occurrence of common childhood infections and periods of more than 10 days of dry cough, chest tightness or wheeze in the children was assessed by annual questionnaires (n = 195 and 184, respectively). Maternal intake of toxicants was estimated from a validated food frequency questionnaire filled in by the mothers at mid-term. The sum of six non-dioxin-like PCBs (PCB 28, 52, 101, 138, 153, 180), and the sum of toxic equivalents of 29 dioxins and dioxin-like PCBs were used. Logistic and linear multivariate regression analyses were performed. Adjustments were made for gender, mode of delivery, Apgar score, breast-feeding, parity, birth season and maternal history of atopy, age, BMI, education and smoking. No associations between prenatal exposure to acrylamide and the health outcomes were found. At age one year, prenatal exposure to PCBs and dioxins was associated with increased risk of wheeze and exanthema subitum, and increased number of upper respiratory tract infections. Similar results were obtained in preliminary analyses for wheeze and upper respiratory tract infections at two years of age. Our findings suggests that prenatal exposure to dioxins and PCBs increase the risk of wheeze and infectious diseases during the first two years of life.
1722 Airborne transmission of respiratory syncytial virus (RSV) infection
Hennant Kulkarni1, Claire Smith1, Robert Hirst1, Norman Baker1, Andreas Easton1, Chris O’Callaghan1. 1Dept. of Infection, Immunity & Inflammation (Division of Child Health), University of Leicester, Leicester, UK; 2School of Life Sciences, University of Warwick, Coventry, United Kingdom

Introduction: RSV is a highly contagious pathogen and spreads among groups of young children, within families and between patients in hospital. RSV is thought to spread predominantly by hands contaminated with respiratory secretions [1]. However, it remains unclear if RSV can be spread by aerosol. Knowledge of this is important as it is assumed in many hospitals that aerosol transmission of RSV does not occur.

Aim: To determine if patients with RSV bronchiolitis produce aerosolised particles containing RSV capable of infecting human respiratory epithelial cells (A549).

Method: 16 infants with “RSV Bronchiolitis” were recruited. An Andersen micro-impactor was placed 10cm from the head of the patient and run for 30min fractionating collected particles into different aerosol size distributions. Room air was impacted into 20ml of RPMI growth media and its infectivity of A549 was measured by the production of fluorescence staining of the infected A549 cells was used to confirm RSV infection.

Results: 17 infants produced infectious airborne particles less than 4.7μ. We estimated the number of infectious RSV within aerosols of less than 4.7μ produced from 12/17 patients to be 188.5±68 (mean ± SEM, range 2.4 to 404±) in 10 litres of air. This volume would be inhaled by a 1.3kg baby in 10 minutes (respiratory rate 40/min; tidal volume 8μl/kg).

Conclusion: Infants with RSV bronchiolitis produce aerosols that contain infectious RSV in aerosols small enough to deposit in the lower airways. These findings may influence infection control strategies to prevent aerosol transmission of RSV in a hospital setting.

Reference:

219. Indoor hazards and respiratory disease: irritants and allergens

1723 Domestic use of hypochlorite bleach and respiratory infections in children
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Introduction: Domestic bleeding sprays, especially window spray, can be a risk factor for airway inflammation, measured as FeNO. This is in agreement with a previous study showing associations between incidence of asthma and domestic cleaning sprays (Zock et al., Am J Respir Crit Care Med, 2007;176:735-741).

Aim: To determine if patients with RSV bronchiolitis produce aerosolised particles containing RSV capable of infecting human respiratory epithelial cells (A549).

Method: 16 infants with “RSV Bronchiolitis” were recruited. An Andersen micro-impactor was placed 10cm from the head of the patient and run for 30min fractionating collected particles into different aerosol size distributions. Room air was impacted into 20ml of RPMI growth media and its infectivity of A549 was measured by the production of fluorescence staining of the infected A549 cells was used to confirm RSV infection.

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Conclusion: Infants with RSV bronchiolitis produce aerosols that contain infectious RSV in aerosols small enough to deposit in the lower airways. These findings may influence infection control strategies to prevent aerosol transmission of RSV in a hospital setting.

Reference:

1724 FeNO in adults in relation to cleaning sprays and other particle generating activities in homes in Scania, Sweden
Gunilla Wierslander, Dan Norback. Department of Medical Sciences, Uppland University, Occupational and Environmental Medicine, Uppsala, Sweden

Aim: To study associations between FeNO and use of sprays and other particle sources at home.

Methods: Easton 106 adults answered a questionnaire on particle sources at home in a larger population survey in Scania, Sweden. Each question had four alterna-
tives on frequency. There were 5 questions on sprays (window, oven, furniture, hair and other sprays), 3 on office equipment (copy machines, laser and inkjet printers), 4 on combustion sources (candles, incense, wood, kerosene) and one on environmental tobacco smoke (ETS). Burning of incense, wood or kerosene was combined to a combustion source index (CSI). Use of office equipment was combined to an office machine index (OMI). Cleaning sprays were combined to a cleaning spray index. Exhaled NO was measured [ NOX MNO (50 ml/min)]. FeNO was log-transformed and associations were analysed by multiple linear regression, adjusting for age, sex, pollen/effurry pet allergy and smoking.

Results: Median FeNO was 17 ppb (IQR 11-22). 14% were above 25 ppb. FeNO was positively associated with cleaning spray index (p=0.047), and use of window spray (p=0.02). No associations were found for FeNO and hair spray, other sprays, ETS, candles, CSI or OMI.

Conclusion: Domestic cleaning sprays, especially window spray, can be a risk factor for airway inflammation, measured as FeNO. This is in agreement with a previous study showing associations between incidence of asthma and domestic cleaning sprays (Zock et al., Am J Respir Crit Care Med, 2007;176:735-741).

1725 Endotoxin levels in primary schools and homes of Dutch school children
José Jacobs, Esmeralda Kroep, Dick Heederik. Environmental Epidemiology, Institute of Risk Assessment Sciences, Utrecht, Netherlands

Background: Indoor air quality is essential for children’s health. Several studies describe the variety and extent of indoor pollutant exposure in homes and to a lesser extent in schools. However studies that include both environments in one study are sparse.

Objective: To assess indoor endotoxin levels in dust and compare levels in primary schools and homes of children.

Methods: This study is an extension of the European HITEA project. Ten schools with moisture/dampness problems (index) and reference schools were selected, based on building questionnaires and on-site inspections. Airborne dust at several locations in school was passively sampled with Electrostatic Collectors (EDC), during 8 weeks in March/April 2010. In the same period, dust was sampled during 2 weeks in 169 children bedrooms from index and reference schools.

Results: Average endotoxin levels ranged from 4355 to 12101 ELISAs in schools, and from 923 to 2570 EU/m³ in homes, adjusted to a two week sampling period. Both school and home endotoxin levels tended to be higher in the index than in the reference category (average ratio~1.35). However, no significant differences were found in the index category, and also within the reference, variation between schools was higher than between both categories. There was less variation between home endotoxin levels within and between both index and reference categories. Classroom occupancy was related to endotoxin levels. Home characteristics associated with endotoxin levels were the number of people living in the house and building age.

Conclusion: Average endotoxin levels were considerably higher in schools than in homes. Occupancy was significantly related with school and home endotoxin levels. Home age also affects endotoxin levels.

1726 The household bio-dust bio-environment and lung function in adult asthma
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Background: The household bio-dust bio-environment includes molds, bacteria, and animal antigens that may affect lung function, especially in asthma.

Methods: Dust from adult asthmatics’ homes was quantified for: Environmental Relative Moldiness Index (ERM), a DNA-based assay reflecting indoor molds; chitin (found in mold cell walls and invertebrate exoskeletons, assayed by blot densitometry); endotoxin (LPS; immulus assay); beta-1,3-glucans (BG, dust mite); and cockroach (CRK) (ELISA). We analyzed Spearman correlations among the exposures. Linear regression tested ERM, chitin, LPS, and BG as predictors of FEV₁, with stratification by greater than/less than a detectable level (>DL) of both DM and CRK.

Results: Data from 72 dwellings were available for all variables. Chitin was significantly correlated with BG (r=0.29; p=0.01) and DM (r=0.33; p<0.01) and weakly (negatively) with both ERM (r=-0.20; p=0.09) and LPS (r=-0.20; p=0.09); BG correlated positively with both DM and CRK (r=0.39 and 0.28, respectively; p<0.05). ERM correlated negatively with CRK (r=-0.31; p<0.01). Adjusting for LPS and BG concentrations, chitin was significantly associated with better FEV₁ (% predicted +4.6% per ng chitin/microgram dust; p<0.001), while ERM was not (r=0.3). Among 37 subjects with DM or CRK >DL, results were similar, but among 35 subjects >DL for DM/CRK, FEV₁ % predicted was positively related to both chitin (+7.5%; p<0.01) and ERM (+2.1% per unit; p<0.05).

Discussion: Chitin and ERM levels may be associated with better FEV₁; the ERM effect may depend on absent DM/CRK co-exposure.

Clinical: In adult asthma, DM and CRK control interventions should consider other potential co-exposures in the complex home bio-environment.

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220. Genes, environment and obstruction

220. Genes, environment and obstruction

1727
Cat, dog and horse allergens in day care centres in Uppsala, Sweden, associations with FeNO and dyspea

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Aim: To study associations between FeNO, FEV1 and dyspepsia in day care centres staff and levels of cat, dog and horse allergens in day care centres.

Methods: In 2009-2010, 5 day care centres in Uppsala participated in a study performed 3 times in each subject in spring, in connection with a diet study. Dust was collected by vacuum cleaning and analysed for cat (Fel d1), dog (Can f1) and horse (Equs cx) allergens by ELISA. Amount of allergens per ALK filter was calculated by multiplying concentration with amount of fine dust. Airborne allergens were sampled in Petri dishes for 1 week. Exhaled NO was measured by NIOX MINO and FEV1 by dynamic spirometry. Dyspepsia was rated from 0-100%. FENO and dyspepsia were log-transformed and associations analysed by multiple linear regression, adjusting for age, atopy, smoking, and body mass index (BMI). All were females.

Results: House dust samples from pets in any building, but all allergens were common. Geometric mean (GM) (ng/g) were 1199 Fel d1, 666 Can f1 and 478 Equs cx. Fel d1 was found in 100% (GM=29.8 ng/mg) and Can f1 in 33% and Ecu c1 in 13% of Petri dish samples. FeNO was higher at amount of Fel d1 (p<0.001) and Can f1 (p<0.01) and lower at higher amount of Equs cx (p<0.11). No associations were found for FEV1 or dyspepsia and allergen levels.

Conclusion: Cat, dog and horse allergens were common in the day care centres, due to track in by clothes or hair. Cat and dog allergens in day care centres can be a risk factor for airway inflammation, measured as FeNO. The negative association for horse allergen remain unclear. It could be due to co-variace with some protective indoor factor, or a healthy life style related to horse riding.

1728
High indoor microbial levels are associated with reduced Th1-cytokine secretion capacity in infancy

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Background: In the early stages of life exposure to microbes and their components may affect the maturation and functions of immune system.

Objective: To examine whether the house dust microbial content is associated with cytokine-producing capacity at birth and at age 1 year.

Methods: Assay of Th1 (IFN-γ) and Th2 (IL-4, IL-5, IL-10) cytokines was performed on buffy coats of 120 children at age 1 year (n=200) following 24h and 48h whole blood stimulation with Staphylococcus enterotoxin A (SEA) and SEB. Geometric mean (GM) (ng/g) were measured using ELISA. Ergosterol (marker for fungal biomass), muramic acid (marker for Gram-positive bacteria) and 3-hydroxy fatty acids (C10:0-C14:0, C15:0, C16:0) were measured using GC. Airborne microbial levels were analysed by high-volume air sampling. To examine whether the house dust microbial content is associated with cytokine-producing capacity at birth and at age 1 year.

Results: A high total level of Gram-positive bacteria in general or Mycobacterium spp. in house dust was associated with decreased SEA-stimulated IFN-γ secretion capacity at birth and at age 1 year. With cytokine-producer capacity at birth and at age 1 year. High indoor microbial levels may affect immune development in early life by reducing Th1-cytokine secretion capacity. In the future, more microbiome studies are needed to better understand the role of microbial exposures on immune development in early life.

Conclusion: Both ETS exposure and SNPs in Gluthatione S-tranferase (GST) genes are associated with FEV1 level. A GSTO2 SNP (rs156997) was associated with FEV1 in a GWAS study (Wilk 2007). We recently found a GSTO1 SNP associated with lower FEV1 in heavy smokers only (≥12.5 pCi; unpublished) suggesting a gene by smoking interaction. Since the GST-family deals with oxidative stress, we hypothesize that GSTO2 SNPs may also interact with ETS exposure and affect lung function.

Methods: Genotypes of individuals (n=8128) from the LifeLines cohort, a general Dutch population cohort, were included. We selected 4 GSTO2 tagging SNPs (MAF=0.10, R2 ~ 0.8) (table 1). Associations between daily hours of ETS exposure (<1 or ≥1 hr), ETS exposure at work (no/yes), history of active smoking (not, recent, and ≥10.5 pCi) SNPs, their recessive model and FEV1 were assessed by linear regression models, adjusted for sex, age, height, weight, and smoking habits.

Results: Daily ETS exposure (≥1 hr=73; ml=0.011) and history of active smoking (≥10.5 pCi =121ml; p<0.001) were associated with FEV1. ETS exposure at work and the SNPs were not significantly associated with FEV1. However, GSTO2 SNPs clearly interacted with ETS exposure and history of active smoking (table 1).

Table 1. GSTO2 by exposure interactions and FEV1 (ml) (95% CI)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>GSTO2</th>
<th>FEV1 (ml) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETS exposure (1 or ≥1 hr/week)</td>
<td>GSTO2: 1</td>
<td>73 (0.011)</td>
</tr>
<tr>
<td>ETS exposure at work (no/yes)</td>
<td>GSTO2: 1</td>
<td>73 (0.011)</td>
</tr>
<tr>
<td>History of active smoking (not, recent, and ≥10.5 pCi)</td>
<td>GSTO2: 1</td>
<td>73 (0.011)</td>
</tr>
</tbody>
</table>

Conclusion: We show that ETS exposure has deleterious effects on FEV1 in subjects homozygous for the minor allele of GSTO2 SNPs.

1730
Genetic overlap of airway obstruction and emphysema

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Airway obstruction and emphysema are two features of chronic obstructive pulmonary disease (COPD). COPD patients can display one phenotype or both at one time. We used the Nelson cohort comprising ~3000 individuals with lung function measurements and CT-scans to determine genes that contribute to both features. We performed genome-wide association studies on both sub-phenotypes. Airway obstruction was investigated in a case-control design (1030 cases with FEV1/FVC < 0.7 and 927 healthy controls). Emphysema was investigated as a quantitative trait. To account for center-derived differences in these measurements we used 15th percentile (p15) of density distribution adjusted for age, sex and height in the trachea. p15 was analyzed using linear regression adjusting for age and pack-years smoking in 3047 subjects. To find overlap between these two sub-phenotypes we selected all SNPs with p<0.001 in each analysis, yielding a total of nine SNPs corresponding to four genes. When these genes were investigated in GeneMania we found that an additional 9 genes directly interacting or co-expressed/co-localized with query genes and two from this point to a drug resistance pathway (GATHER p<0.001, Bayes factor 6).

This is an interesting approach that can help identifying a shared etiology of two distinct sub-phenotypes of a single complex disease.

1731
Susceptibility to chronic mucus hypersecretion: A genome-wide association study

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Background: Patients with COPD with chronic mucus hypersecretion (CMH) have a significantly increased FEV1 decline and a higher risk of hospitalization...
than those without CMH. Moreover, although individuals with CMH are more likely to be ex- or current smokers, so far it is unclear why some smokers develop CMH and others do not. A plausible explanation for this phenomenon would be a genetic predisposition.

Methods: We performed a genome wide association study (GWAS) using the Nelson study (a population-based lung cancer screening study from Groningen and Utrecht, the Netherlands) including 717 subjects with and 1,795 without CMH, all ex or current heavy smokers (>20 pack years). Lung function results and information about spumt expectoration during the previous year were collected at the start of the study. To enhance power we added 590 blood bank controls. Genotyping data were analyzed using PLINK with adjustment for center (Groningen/Utrecht). We aimed to replicate the results by evaluating the top single nucleotide polymorphisms (SNPs) in 7 European cohorts contributing 487 cases and 1,118 controls.

Results: We identified 77 SNPs associated with CMH with a p-value <10^-6, of which 5 SNPs had a p-value <10^-10. Meta-analysis of selected top SNPs in the initial and replication cohorts identified 3 SNPs with a p-value <10^-10 and 3 with a p-value <10^-15. Some genes close to these SNPs have been reported to be associated with epithelial changes.

Conclusion: This study suggests that susceptibility to CMH is associated with genetic predisposition. To confirm these data replication will be extended to 3 additional cohorts.

1732 Common variant of gasterminder-like gene, fetal and early life smoke exposure and the risk of asthma-like symptoms in preschool children
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Rationale: Single nucleotide polymorphisms (SNPs) in the region of gasterminder-like (GSDML) gene on chromosome 17q12-1q41 are associated with increased risks of childhood-onset asthma. These risks seem to be modified by environmental tobacco smoke.

Objectives: To assess whether the associations of GSDML with asthma-like symptoms are modified by smoke exposure, both during fetal and in early life.

Methods: This study was embedded in the Generation R Study, a population-based birth cohort study from fetal life onwards in the Netherlands. We genotyped GSDML (rs2305480) and assessed maternal smoking repeatedly during pregnancy and smoke exposure in early life at the age of 2 years by questionnaires. Asthma-like symptoms were reported by parents at the ages 1, 2, 3 and 4 years.

The analyses were based on 2,025 Caucasian children with complete data.

Results: GSDML was associated with asthma-like symptoms at the ages of 2, 3, 4 and 4 years (overall Odds Ratio 1.15 (1.06, 1.26)). The GSDML effect on asthma-like symptoms was stronger among children who were exposed to smoke during fetal life (p interaction=0.030). Smoke exposure in early life also tended to increase the effect of GSDML on asthma-like symptoms, but the test for interaction was not significant (p interaction=0.240). The modifying effects by fetal and smoke exposure in early life were independent. The strongest effects were present in children aged 3 and 4 years with both the risk-allele and smoke exposure during fetal and early life.

Conclusion: GSDML is associated with asthma-like symptoms in preschool children, and this association seems to be modified by fetal and smoke exposure in early life.

1733 Interactions between current tobacco smoke exposure and GSTP1 on lung health outcomes at 6, 12 and 18 years
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Background: Maternal history of asthma is among the most consistently reported risk factors for asthma in children. Furthermore, a number of studies suggest that mitochondrial dysfunction plays a role in the pathogenesis of asthma. Until now, it was never investigated whether an implication of mitochondrial tRNA gene mutations in asthma patients: the role of the mitochondrial genome in the etiology of asthma we analyzed the mitochondrial tRNA genes, and part of their flanking regions, in 26 unrelated patients with asthma and we compared the findings with a set of 60 healthy controls.

Results: We found a total of 10 mutations in 19 out of 26 asthmatic patients. Four of the mutations (595insC in tRNA^Glu^, A8343G in tRNA^Glu^, T10448C in tRNA^Glu^ and G709A in 12S rRNA) were not found in the control group. Five mutations were observed in controls but in a significantly lower rate: 3.3%, vs. 27% (A12308G in 12S rRNA), 10% vs. 57.7% (A750G in 12S rRNA). The modifying effects of tobacco smoke exposure on lung health outcomes. Other GSTs or detoxification pathways may play a more important role in modifying the effects of tobacco smoke (passive/active) at 12 and 18 years in this study cohort. Funding: NHRMC.

Conclusions: Mitochondrial tRNA and tRNA mutations are more frequent in asthma patients than controls. However, it is certain that further studies in larger cohorts are needed to confirm these observations.
211. Obstructive sleep apnoea: the heart and the brain

P1737
Transvenous phrenic nerve stimulation improves Cheyne-Stokes respiration in patients with chronic heart failure
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Background: Cheyne-Stokes respiration (CSR) may accelerate progression of congestive heart failure (CHF) and is associated with poor survival. Phrenic nerve stimulation (PNS) may interrupt CSR and improve CHF outcomes. We report the preliminary findings of a randomized controlled study of patients with CHF with severe CSR who were randomized to a single transvenous PNS lead placement versus control. CSR was defined as two or more events per hour of sleep with a difference of more than 20 breaths per minute between the end of inspiration and the end of expiration.

Methods: Thirty-five patients with severe CSR (apneahypopnea index (AHI) >20 events per hour of sleep) were randomized to PNS or control. PNS was performed using the Eupnea System software. Respiratory properties were assessed prior to and post-PNS. PNS was assessed at a maximum of 10 mA.

Results: Mean values of TO was significantly higher in the PNS group than in the control group (p < 0.001). The mean values of TS were not significantly different between the two groups. The value of TO was positively correlated with the value of TO (r = 0.845, p < 0.001).

Discussion: As the OSAS worsens, the cardiac rhythm disorders become more prominent. The impairment of cardiovascular autonomic system in OSAS patient without CAD may be a possible component of deleterious effect of OSAS.

Conclusion: The impaired autonomic cardiac control may in part explain the mechanisms promoting arrhythmias and sudden death in OSAS subjects. To achieve a meaningful reduction in mortality, OSAS must be targeted for treatment.

P1738
Heart rate turbulence: In patients with obstructive sleep apnea without coronary artery diseases
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Background: Obstructive sleep apnea syndrome (OSAS) is a common disorder associated with an increased risk of cardiovascular disease and stroke. This study was conducted to demonstrate the effects of OSAS on baroregulatory function by using heart rate turbulence (HRT) parameters.

Methods: Sixty four OSAS patients without coronary artery disease (CAD) and 30 healthy subjects were enrolled in this study. HRT analysis (TO: turbulence onset and TS: turbulence slope) was obtained from 24-hour ECG recordings. The values of HRT were compared between two groups along with basic clinical, echocardiographic and Holter parameters. Besides, the relationship between HRT and apnea-hypopnea index (AHI) was analyzed.

Results: The mean values of TO was significantly higher in the OSAS group than in the control group (p < 0.001). The mean values of TS were not significantly different between the two groups. The value of AHI was positively correlated with the value of TO (r = 0.845, p < 0.001).

Discussion: As the OSAS worsens, the cardiac rhythm disorders become more prominent. The impairment of cardiovascular autonomic system in OSAS patient without CAD may be a possible component of deleterious effect of OSAS.

Conclusion: The impaired autonomic cardiac control may in part explain the mechanisms promoting arrhythmias and sudden death in OSAS subjects. To achieve a meaningful reduction in mortality, OSAS must be targeted for treatment.
P1740
Neurocognitive disorders in children with sleep-disordered breathing
Alessandra Tabarrini, Maria Chiara Paulino, Laura Papini, Rosa Castaldo, Francesco Biagiarelli, Raffaella Bruschi, Martina Forlani, Maria Pa Villa.
NESTOS Department, Pediatric Unit. S. Andrea Hospital, Faculty of Medicine and Psychology, University La Sapienza, Rome, Italy

Aims: To compare the presence of neurocognitive disorders in children with Obstructive Sleep Apnea Syndrome (OSAS) or Primary Snoring (PS) and normal controls, and to investigate their correlation with duration of Sleep-Disordered Breathing (SDB).

Methods: 137 subjects (M/F 70/67; mean age 9.47±2.35 yrs) were studied: 58 children with SDB (19% P9.43±1% minimum OSAS.37.9% moderate-severe OSAS and 3.5% severe OSAS), 30 healthy children, 30 normal controls (M/F 15/15; age 9.47±2.35 yrs), and 10 children with Primary Snoring (M/F 5/5; age 9.47±2.35 yrs). Subjects underwent clinical evaluation, polysomnography and neurocognitive assessment based on Wechsler Intelligence Scale for Children (WISC-R). The control group was studied through a medical questionnaire and WISC-R.

Results: Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full-Scale Intelligence Quotient (FSIQ) were lower in SDB group than in control children (VIQ 94.55±13.74 vs 115.84±10.63; PIQ 100.10±13.25 vs 118.24±11.66 vs 110.04±11.66; FSIQ 76.73±10.00). On the basis of the presence of cognitive impairment (defined arbitrarily as a FSIQ < mean FSIQ standard population – 2SD), SDB group was subdivided in: Group A: 15 children with SDB and cognitive impairment; Group B: 43 children with SDB without cognitive impairment. The age of onset was earlier in Group A than in Group B (3.64±2.65 yrs vs 5.29±3.64 yrs; p<0.05); duration of disease was longer in group A than in Group B (5.21±2.57 yrs vs 3.44±2.42 yrs; p<0.05).

Conclusions: The incidence of neurocognitive disorders was greater in children with SDB than in controls. A significant correlation was present between neurocognitive impairment and both SDB’s age of onset and duration of disease suggesting that early onset and a long duration of disease are the major risk factor.

P1741
Mean platelet volume in obstructive sleep apnea patients. Another link to cardiovascular disease?
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3Department of Microbiology, University Hospital of Alexandroupolis, Greece; 1Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece; 2Department of Microbiology, University Hospital of Alexandroupolis, Alexandroupolis, Greece

Objectives: To evaluate the Mean Platelet Volume (MPV) as a potential marker of cardiovascular risk in patients with Obstructive Sleep Apnea (OSA) and cardiovascular risk. Mean Platelet Volume (MPV) is a potential marker of cardiovascular risk in OSA patients. A large number of studies has addressed the association between MPV and cardiovascular risk in OSA patients. However, there is a lack of evidence regarding the association between MPV and cardiovascular risk in OSA patients.

Materials and methods: This study included 697 subjects with suspected sleep disorder for the presence of arrhythmia. The study comprised 257 OSA patients and 99 non-OSA patients (controls). OSA patients had a mean age 47.9±13.5 years, body mass index of 35.7±9.5 kg/m2, apnea hypopnea index (AHI) of 42-4±36.9/hr, and males represented 60.7% of the group. The prevalence of arrhythmia in OSA patients was higher than that in the non-OSA group (24.5% vs. 12.1%, p = 0.01). Among OSA patients, prematurity, atrial fibrillation was present in 10.1%, premature ventricular contraction in 16.3% and atrial fibrillation in 4 patients (1.6%). OSA patients with arrhythmias were significantly older (53.5±15.3 years vs. 46.1±12.4 years; p<0.05), heavier (38.3±9.1 kg/m2 vs. 34.9±6.9 kg/m2; p<0.05), had lower average nocturnal oxygen saturation (92.1±3.6% vs. 91.4±3.5%; p<0.05), and spent longer time with 0% saturation (<90% (22.6±31.6 minutes vs. 11.2±25.2 minutes; p<0.05). OSA patients with arrhythmias had a higher prevalence of hypertension and ischemic heart disease. Multivariate logistic regression analysis identified arrhythmias as the only predictor of arrhythmias (OR 2.36; CI 1.004-5.59; p<0.05).

Conclusions: Arrhythmias were more prevalent among OSA patients with longer periods of hypoxemia and those with ischemic heart disease.

P1714
Effects of auto-servo ventilation on cardiovascular function in patients with congestive heart failure and sleep-disordered breathing – A multicenter randomised controlled trial
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Objectives: to study the effects of Auto-servo ventilation (ASV) on left ventricle function in patients with congestive heart failure (CHF) and sleep-disordered breathing (SDB).

Methods: This study was designed to evaluate the effects of ASV on left ventricle function in patients with CHF and SDB. The study was performed in a multicenter randomized controlled trial. Patients were randomly assigned to either ASV or CPAP treatment (BiPAP autoSV, Philips-Respironics). Polysomnographic recordings were obtained in all patients to assess the severity of SDB and to determine the best treatment for each patient. Patients were followed up for 2 months, and the primary endpoint was the change in LVEF. The secondary endpoints were the changes in NT-proBNP levels and the changes in daytime activity.

Results: Significantly larger reduction in AH1 was observed in the ASV group (average daily ASV use was 4.71±2.93 hours/day) than in the control group (-3.91±1.6 hours/day, p<0.05). Both groups showed similar significant increase of LVEF (+3.4±4.5% vs. +3.5±5.6%, p<0.05). In ASV group the reduction of NT-proBNP (-360.5±697.1 vs. +367.8±652.1 ng/ml, p<0.05) and the increase of daytime activity duration (+14±5.2 vs. -24±4.1 hours, p<0.05) were significantly greater than in the control group (-15.4±4.9 vs. +25.0±3.4 hours, p<0.05). The increase of LVEF (+3.4±4.5% vs. +3.5±5.6%, p<0.05) was significantly greater in ASV group than in the control group (+25.0±3.4% vs. -15.4±4.9 hours, p<0.05).

Conclusions: ASV in CHF patients with SDB reduces NT-proBNP levels as a surrogate for improvement of cardiac function. Such changes were not associated with significant changes in LVEF. Patients on ASV improved their activity periods during the day and some days of QOL.

P1744
Effect of auto servo-ventilation (ASV) and continuous positive airway pressure (CPAP) on B-type natriuretic peptide (NT-proBNP) in patients with co-existing obstructive (OSA) and central sleep apnea (CSA) in heart failure (HF)
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Introduction: The optimal ventilatory mode for patients with co-existing OSA and CSA in HF is unclear. We investigated the effects of ASV and CPAP therapy on NT-proBNP, a marker of HF severity.

Methods: 70 patients (66±3±9±1 yrs., 31±6±0±6 kg/m2) with <80% Cheyne-Stokes respiration and 20±5% obstructive disturbances were randomly assigned to either ASV or CPAP treatment (BiPAP autoSV, Philips-Respironics). Polysomnographic parameters and NT-proBNP levels were measured at baseline and after 12 months. Data of patients who used their device during the whole period were analyzed (26 ASV, 25 CPAP). For further analysis, patients were divided into responders (AHI<10/h and 50% below baseline AHI) and non-responders.

Results: AH1 significantly improved in both groups (ASV: 48±2±5.0 vs. 6.9±6±8.6%; p<0.001, CPAP: 41±6±15.4 vs. 11±4±6.6%, p<0.001). ASV was superior in reducing central disturbances (5±0±5.9 vs. 9±1±8±2, p<0.03). NT-proBNP was similar at baseline and improved after 12 months only in the ASV group (ASV: 537±892 vs. 21±3±515 ng/L, CPAP: 687±979 vs. 876±1882 ng/L).
Sleep apnea was linked with HT independently of other cardiovascular complications like hypertension and cardiac failure in 3093 obese patients (IMC ≥ 30kg/m2) referred for suspicion of OSA and SAHS and stroke. CPAP compliance and new stroke events were recorded in addition to ventricular arrhythmias and cardioversion events. The use of occlusal splint can change autonomic cardiac modulation in bruxers.

Conclusion: Children with CCHS are at risk to develop neurocognitive deficits, especially in memory, attention and visuospatial treatment. Factors underlying these abnormalities are to be determined. Neurocognitive monitoring should be included in long-term follow-up of CCHS.

Introduction: Sleep bruxism was recently classified as a sleep related movement disorder and it has been linked to emotional alterations, arousals and neurological symptoms. Objective: To evaluate the alteration in heart rate variability (HRV) in bruxers prior and after 1 month of occlusal splint (OS) usage. Methods: Thirteen consecutive patients were enrolled in the study. Patients with current CPAP use and group 2, patients with no CPAP treatment. All TMD symptoms were decrease after first month of OS usage. The HRV assessed by NES showed that the RR interval improved from 801 ±28.0 to 833 ±30.0 but was not significant. The frequency-domain parameter was not significant for both Fast Fourier Transform and Wavelet spectral method in both parasympathetic and sympathetic area. Low frequency and High frequency did not alter post first month of OS usage.

Results: Oclusal splint reduced all TMD symptoms related prior treatment. HRV was not changed, maybe due to the short period of the study, one month, of OS usage. Further evaluation with a longer period of treatment is needed.

Sleep bruxism was recently classified as a sleep related movement disorder and it has been linked to emotional alterations, arousals and neurological symptoms. Objectives: To evaluate the alteration in heart rate variability (HRV) in bruxers prior and after 1 month of occlusal splint (OS) usage. Methods: Thirteen consecutive patients were enrolled in the study. Patients with current CPAP use and group 2, patients with no CPAP treatment. All TMD symptoms were decrease after first month of OS usage. The HRV assessed by NES showed that the RR interval improved from 801 ±28.0 to 833 ±30.0 but was not significant. The frequency-domain parameter was not significant for both Fast Fourier Transform and Wavelet spectral method in both parasympathetic and sympathetic area. Low frequency and High frequency did not alter post first month of OS usage.

Results: Oclusal splint reduced all TMD symptoms related prior treatment. HRV was not changed, maybe due to the short period of the study, one month, of OS usage. Further evaluation with a longer period of treatment is needed.
group 1 was 16 (26%) and 11 (23%) in group 2; they were not significant statistic differences (p=0.72). The statistically significant variables in multivariate analysis were neck circumference OR [0.87 (IC95% 0.76-0.99; p=0.04)] and BMI OR [0.86 (IC95% 0.75-0.98; p=0.021)]. The survival analysis results are:

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age (± SD)</th>
<th>Median survival</th>
<th>P (Log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>62.65±0.76</td>
<td>64.04±12.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Group 2</td>
<td>64.04±12.6</td>
<td>64.04±12.6</td>
<td>0.012</td>
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</tbody>
</table>

The stroke event free time until new event in group 1 was 31.4 months ± 22.6 SD, and in group 2, 25.3 months ± 13.9 SD, without statistical significance.

Conclusions: New stroke development is not associated with CPAP compliance, however it seems to have longer survival probability in CPAP compliant patients.

P1750

Gender-dependent characteristics of sleep-disordered breathing in chronic heart failure

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Background: Sleep-disordered breathing (SDB) is common in patients with chronic heart failure (CHF) and influences the progression of the disease. Large multicenter studies are lacking.

Methods: In the ongoing prospective multi-center SchlaHF registry we studied so far 1,273 CHF patients diagnosed by gold standard polysomnography (PSG). New York Heart Association (NYHA) class was ≥II and left-ventricular ejection fraction (LVEF) ≤45%. Patients were screened with a two-channel device and referred to a sleep laboratory in case of suspected SDB. Using PSG we studied sleep and SDB characteristics in these referred CHF patients. SDB was defined as apnea-hypopnea index (AHI) >15/h.

Results: Gender-dependent sleep efficiency was similar in chronic sleep apnea (CSA) (m: 75.6%, f: 76.2%, n.s.), obstructive sleep apnea (OSA) (m: 73.8%, f: 70.4%, n.s.) and in patients without SDB (m: 76.0%, f: 73.9%, n.s.). The same results we found for sleep duration in CSA (m: 317min, f: 324min, n.s.), OSA (m: 38.0h, f: 34.9h, n.s.) and in patients without SDB (m: 3.7h, f: 3.2h, n.s.). Significant gender-dependent differences were found in the respiratory subindices: apnea-index (AI) in CSA (m: 23.8h, f: 14.5h, p<0.05), OSA (m: 22.4h, f: 14.5h, p<0.05) and in patients without SDB (m: 3.7h, f: 3.2h, n.s.).

Conclusions: In the SchlaHF registry sleep duration and sleep efficiency were similar both in men and women regarding CSA, OSA and patients without SDB. Gender-dependent differences were found in the subindices AI and HI.

P1751

The impact of obstructive sleep apnea syndrome on cardiovascular system in children

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Introduction: Obstructive Sleep Apnea Syndrome (OSAS) has been shown to be an independent risk factor for cardiovascular disease in adults. However, few data are known about the effect of OSAS on cardiovascular system in children.

Aims: To investigate clinical and laboratory parameters associated with cardiovascular disease in children with OSAS.

Methods: Seventeen subjects, aged 5 to 12 years (mean age 9.2±4.2 years), referred for evaluation of systematic snoring (<4 nights/week), underwent overnight polysomnography: evaluation of blood pressure, lipidic profile and comprehensive echocardiographic assessment. According to the Apnea Hypopnea Index (AHI) subjects were divided into three groups: A. no snoring (AHI<1, n=1), B. mild OSAS (AHI= 1-5, n=12), C. moderate-severe OSAS (AHI >5, n=4).

Results: There were no significantly differences in age, sex, heart rate, systolic and diastolic blood pressure and lipidic profile among the groups (p>0.05). Right ventricular dimension (Right Ventricular end-Diastolic dimension - RVDD) and left ventricular dimensions (Left Ventricular end-Diastolic dimension - LVDd, Left Ventricular diastolic mass - LVdmass, Left Ventricular Posterior Wall diastolic –LVPWD, IntraVentricular Septum diastolic – IVSd) were not statistically significant different between the three groups and were within normal limits. RVDD was higher in OSAS patients (p=0.096) than in controls.

Conclusions: The present study suggests that young patients with systematic snoring have no echocardiographic evidences of cardiac dysfunction. Nevertheless, less is a correlation of increased right ventricular dimension, although not statistically significant, in patients with OSAS.

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Effect of disease severity on heart rate recovery following laboratory and field exercise testing in patients with obstructive sleep apnea (OSA): A comparative study

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Introduction: It is known that patients with Obstructive Sleep Apnea (OSA) have increased activity of the sympathetic nervous system and decreased activity of the parasympathetic nervous system. Heart rate recovery in the first minute after exercise (HRR) is often used as an index to stratify risk factor for cardiovascular mortality in OSA patients.

Methods: We studied twenty five patients by polysomnography in the laboratory. Ten patients diagnosed with moderate OSA (15≤AHI<30), 10 patients diagnosed with severe OSA (AHI≥30) and 5 patients were normal (AHI<5). HRR following cessation of incremental exercise to the limit of tolerance on the cycle ergometer and after termination of a six minute walking test (6MWT) was assessed by a Nonin pulse oximeter worn on the wrist in all patients and controls.

Results: There was a significant difference in HRR; after the maximal incremental test among severe and moderate OSA patients and healthy controls (18±5 and 25±5 and 34±4 beats/min, respectively). Similarly, HRR, after the 6MWT was different between the two patient groups (severe by 15±5 and moderate by 19±4 beats/min and normal subjects (28±5). There was no difference in the magnitude of HRR, between the exercise tests among the three groups.

Conclusion: The more advanced the disease severity of OSA the slower was the recovery of heart rate after the exercise. The 6MWT reflects equally well to the incremental maximal test the sluggishness in heart rate recovery and hence it can be used alternatively to the maximal exercise test to detect the likelihood of cardiovascular risk in patients with OSA.

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Impact of obstructive sleep apnea on diastolic function

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The association of obstructive sleep apnea (OSA) with diastolic dysfunction is unclear. We investigated whether OSA independently affects diastolic function in a primary care cohort of patients with cardiovascular risk factors. 378 study participants with risk factors for diastolic dysfunction (e.g. hypertension, diabetes, heart failure) from the germanwide DIAST-CHF cohort were prospectively included into this substudy and a polygraphy was performed in all patients. Diastolic dysfunction was assessed by comprehensive echocardiography including tissue Doppler. Patients with more episodes of central sleep apnea than obstructive sleep apnea were excluded from further analysis (n=14). In the remaining subjects, 22.8% had an AHI >15. The prevalence of diastolic dysfunction increased from 75.0% (none) to 81.8% (mild) to 90.2% (severe sleep apnea), p=0.020. The degree of diastolic dysfunction also increased with sleep apnea severity. In univariate regression analysis, age, AHI > 15, heart rate, body mass index, systolic blood pressure and left ventricular mass were associated with diastolic dysfunction. In multivariate regression analysis, only age, AHI > 15 and heart rate were independently associated with diastolic dysfunction.

Conclusion OSA is independently associated with diastolic dysfunction in patients with risk factors for diastolic dysfunction.

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Early cardiovascular disease markers in “healthy” OSA patients are related with sympathetic activity

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Rationale: Obstructive sleep apnea syndrome (OSAS) is associated with high sympathetic activity (SA) and a subsequent risk of hypertension and atheroscle-
Comorbidities and impact on society of asthma and COPD

P1755
Development and validation of a new comorbidity index for COPD
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Comorbidities influence outcome in COPD, but their role remains poorly described. We studied the impact on survival of COPD related comorbidities and developed a COPD specific comorbidity (COTE) index. We also compared COTE with the Charlson Comorbidity Index (CCI) and BODE.

Methods: We followed 1664 COPD subjects for over 4 years. Systematically, 80 possible comorbidities were recorded including conditions listed in CCI. In a randomly selected 2/3 of the cohort we calculated their prevalence. Using Cox proportional hazard, 6 of these comorbidities were independently associated with mortality. We then assigned points to the 6 comorbidities and constructed the COTE index based on likelihood ratios for death.

Results: 23 of 80 comorbidities differed in prevalence between survivors and nonsurvivors. The COTE index was superior to Charlson in mortality prediction: HR (95%CI) of [1.22 (1.17,1.27, p<0.001) vs. 1.03 (0.99,1.07, p =0.126)] and complementary to BODE [1.32 (1.28,1.36, p < 0.001)].

Conclusion: Comorbidities are prevalent in COPD and a subset of them influence survival. The COTE is simpler and more accurate than the Charlson index in predicting survival. The COTE adds independent predictive power to the BODE index.

P1756
Association between lung function and subclinical atherosclerosis in obese subjects
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An association between COPD and subclinical atherosclerosis that persisted after adjusting for cardiovascular risk factors has been reported. This may explain the excess cardiovascular mortality seen in patients with COPD.

Objective: To investigate the association between lung function and subclinical atherosclerosis in a population of obese adults with a normal lung function.

Methods: This is a cross-sectional analysis of the NIGG (Netherlands Epidemiology of Obesity) study, a cohort of adults aged 45 to 65 years with a Body Mass Index (BMI) 27> kg/m2. The association between FEV1 and subclinical atherosclerosis (mean maximal common carotid intima-media thickness [cIMT] measured by ultrasound) was assessed using linear regression.

Results: 1115 adults were included with a mean (25th-75th percentiles) age of 56 (51-61) years, BMI of 31 (28-32) kg/m2, FEV1 of 104% (94-113) and 48.7% men. One percent FEV1% increase was associated with 0.001 mm (95% CI -0.001, -0.002) decrease in mean maximal cIMT.
Fatigue in COPD and the impact of heart disease comorbidity: A population-based study

Fatigue is a common symptom among people with COPD. However, there are few studies describing fatigue in COPD and the impact of comorbidity, none of them population based.

**Background:** Fatigue is a common symptom among people with COPD. However, there are few studies describing fatigue in COPD and the impact of comorbidity, none of them population based.

**Aim:** To describe fatigue in COPD by disease severity according to GOLD, and the impact of self-reported heart disease.

**Methods:** The Functional Assessment of Chronic Illness Therapy (FACT-T). Fatigue scale was used to assess fatigue; lower scores represent worse fatigue (0-52). Data were collected in 2007 from the Obstructive Lung Disease in Northern Sweden (OLIN) COPD cohort; 564 subjects with COPD, with a distribution of disease severity representative for the general population, and 786 non-COPD subjects.

**Results:** Median FACT-T score was 44.0 in COPD subjects, significantly lower compared to 46.0 in non-COPD (p=0.006). Score decreased by disease severity: stage I: 46.0, stage II: 43.7, and stage III-IV: 40.0. There was no significant difference between stage I and non-COPD.

**Conclusions:** Fatigue increases with GOLD-defined disease severity, but the score is not significantly different from non-COPD until stage II. Heart disease increases fatigue in both COPD and non-COPD.

**P1759 Reduced lung function is an independent risk factor for the development of impaired glucose tolerance?**

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**Objectives:** Reduced pulmonary function is a risk factor for the development of impaired glucose tolerance (IGT) but has yet to be determined. The aim of the present study is to obtain more information on this point in Japanese males.

**Methods:** First, 975 men showing normal lung function without respiratory disease were recruited in cross-sectional research. All the subjects were divided into quartiles according to baseline%FVC,%FEV1, and FEV1% and analyzed the ratio of IGT and DM. Next, 511 men showing normal lung pattern in 75g OGTT were recruited in longitudinal research. The subjects were divided into%FVC,%FEV1, and FEV1% quartiles, we compared the cumulative incidence rates of IGT among the four groups, and analyzed the risk factors for the development of IGT.

**Results:** In the cross-sectional research, the rates of IGT and DM for each quartile at first examination were significantly associated with lower%FVC and%FEV1 quartile, but not significantly with lower FEV1% quartile. During the mean follow-up period of 28.4±6.0 months, 89 (17%) among 511 normal glucose tolerance (NGT) subjects developed IGT during this period. The cumulative incident rates of IGT for each quartile were significantly higher in lower%FVC and%FEV1 group, but not significantly with lower FEV1% quartile. In a Cox proportional hazards model, only lower%FVC quartile was an independent risk for development of IGT adjusted for age, BMI, systolic BP, total cholesterol, CRP, and pack-year smoking.

**Conclusions:** Not reduced%FEV1, and FEV1% but reduced%FVC is an independent risk factor for the development of IGT in Japanese males.

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**P1760 Lung function, bronchial hyperresponsiveness (BHR) and metabolic risk factors in adults: Preliminary results from the gene environment interaction in respiratory disease (GEIRD) survey**

Lucia Cazzolletti1, Giuseppe Verlato1, Simone Accordini1, Cristina Bombieri2, Veronika Cappa1, Pietro Ferrari2, Kai Schenk2, Alessandro Marconi1, Mario Olivieri1, Elisabetta Zanolin1, Roberto de Marco1, Marcello Ferrari3, 1Department of Public Health and Community Medicine, University of Verona, Verona, Italy; 2Department of Life and Reproduction Sciences, University of Verona, Verona, Italy; 3Unit of Occupational Medicine, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

**Background:** Lung function is a risk factor for cardiovascular events and mortality, and is associated with insulin resistance and type 2 diabetes mellitus. It is well known that a common mechanism, such as insulin resistance and obesity, underlie metabolic syndrome (MS).

**Methods:** Our aim was to assess the association between lung function and MS in the GEIRD study, a nested multi-case control survey, in Verona, Italy. The study population included 1117 subjects (aged 20-66 years) who underwent spirometry (n=1117) and methacholine challenge (n=472). MS was defined according to the presence of 3 or more of the following factors: blood pressure of 130/85 mmHg or higher, abdominal obesity (waist girth: men>102, women>88 cm), self reported dyslipidemia, self reported diabetes. We studied the association of FEV1, FVC (% predicted), FEV1/FVC (% predicted) and BMI (% predicted) with MS and each of its components (using multiple linear or logistic regression adjusted for sex, age, height, smoking habits and case-control status). MS was associated with reduced FEV1 predicted (b=3.4, 95%CI: -6.5, 0.2), but not with FEV1/FVC (% predicted) (b=0.2, 95%CI: -1.6, 1.2). A negative but not statistically significant association between FEV1 and FVC (% predicted) was found. A positive association emerged between BMI and BHR (OR=8.79, 95%CI: 2.3-33.8). Among MS components, only abdominal obesity was related with a reduced FVC (% predicted) (b=-3.5, 95%CI: -6.0, 0.0).

**Conclusions:** The study results represent the low FEV1% predicted and BHR are associated with MS. The results of the present analysis deserves further investigation.

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**P1761 Atopic status affects association between bronchial hyperresponsiveness and asthma symptoms in females**

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**Background:** Bronchial hyperresponsiveness (BHR) is associated to asthma. Our objective was to analyse if atopic status and gender affected the associations between asthma symptoms and the extent of BHR.

**Methods:** In a Danish cross-sectional study of asthma in subjects aged 20-44 years (ERCHS protocol) 933 subjects were eligible for analysis. Asthma symptoms were defined by an 8 items asthma score (Pekkanen, J. et al, Eur. Respir. J. 2005; 19(5):953-61)
Results: Atopy was present among 181 (36%) females and 192 (45%) males (χ²-test, p<0.001). LDS was higher among atopic subjects compared with the non-atopic (t-test, p<0.001). Figure 1 shows associations between LDS and asthma score by gender and atopic status.

Conclusion: Currently there is some inconclusive evidence suggesting an effect of asthma on increased caries.

Methods: An Ovid Medline database search was performed from 1950 through May 2010 using the MeSH terms "asthma" and "caries". Summary effect estimates were calculated with fixed- and random-effects models and determinants of heterogeneity were studied in meta-regression analysis.

Results: The meta-analysis was based on 11 articles providing effect estimates of asthma on primary dentition and 14 articles on permanent dentition. The summary effect estimates of the relation between asthma and caries from the random-effects models and determinants of heterogeneity were studied in meta-regression analysis.
P1767

Short-term air pollution triggers acute rejection after lung transplantation

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Background: In a population-based cross-sectional asthma survey, 6,950 (70%) individuals aged 20-44 completed an extended ECRHS screening questionnaire. Subjects with current asthma were identified by questions on currently taking any asthma medication, having had an attack of asthma or doctor diagnosed asthma plus asthma-like symptoms during the last 12 months. Employment status was determined by means of multiple regression models. The productivity costs due to absenteeism were estimated using the human capital approach. Results: The prevalence of current asthma was 7.7% in males and 10.6% in females. The total average annual extra costs per asthmatic subject in comparison with non-asthmatic subjects were € 2,081 and € 1,922 for males and females, respectively. Productivity costs were the major component accounting for 85% in males and 70% in females. Hospital care expenditures accounted for the greatest percentage of the direct costs in both gender. We extrapolated the average annual costs associated with current asthma to € 352 million in the entire Danish population aged 20-44. Conclusions: The economic burden of asthma in Denmark is substantial and primarily due to productivity costs accounting for three quarters of the total costs.

P1769

Health-related quality of life in subjects with respiratory diseases: Preliminary results from the GEIRD study

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Introduction and background: Asthma is often associated with health deterioration and reduced working capacity resulting in health-related and productivity costs. Population-based studies on the economic burden of asthma on society and individuals are limited. Aims and objectives: To estimate the extra costs to society due to adult asthma in Denmark. Methods: In a population-based cross-sectional asthma survey, 6,950 (70%) individuals aged 20-44 completed an extended ECRHS screening questionnaire. Subjects with current asthma were identified by questions on currently taking any asthma medication, having had an attack of asthma or doctor diagnosed asthma plus asthma-like symptoms during the last 12 months. Employment status was defined by current or last held job. The analyses were based on data on individual level extracted from national registers. The direct (health care) costs were estimated by means of multiple regression models. The productivity costs due to absenteeism were estimated using the human capital approach. Results: The prevalence of current asthma was 7.7% in males and 10.6% in females. The total average annual extra costs per asthmatic subject in comparison with non-asthmatic subjects were € 2,081 and € 1,922 for males and females, respectively. Productivity costs were the major component accounting for 85% in males and 70% in females. Hospital care expenditures accounted for the greatest percentage of the direct costs in both gender. We extrapolated the average annual costs associated with current asthma to € 352 million in the entire Danish population aged 20-44. Conclusions: The economic burden of asthma in Denmark is substantial and primarily due to productivity costs accounting for three quarters of the total costs.

To our knowledge, this is the first study to perform a direct and simultaneous comparison of quality of life in several respiratory disorders. Subjects who suffered from COPD, current asthma and ORC had poorer HRQL than controls.

P1770

The costs of adult asthma in Denmark

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Background: Asthma is often associated with health deterioration and reduced working capacity resulting in health-related and productivity costs. Population-based studies on the economic burden of asthma on society and individuals are limited. Aims and objectives: To estimate the extra costs to society due to adult asthma in Denmark. Methods: In a population-based cross-sectional asthma survey, 6,950 (70%) individuals aged 20-44 completed an extended ECRHS screening questionnaire. Subjects with current asthma were identified by questions on currently taking any asthma medication, having had an attack of asthma or doctor diagnosed asthma plus asthma-like symptoms during the last 12 months. Employment status was defined by current or last held job. The analyses were based on data on individual level extracted from national registers. The direct (health care) costs were estimated by means of multiple regression models. The productivity costs due to absenteeism were estimated using the human capital approach. Results: The prevalence of current asthma was 7.7% in males and 10.6% in females. The total average annual extra costs per asthmatic subject in comparison with non-asthmatic subjects were € 2,081 and € 1,922 for males and females, respectively. Productivity costs were the major component accounting for 85% in males and 70% in females. Hospital care expenditures accounted for the greatest percentage of the direct costs in both gender. We extrapolated the average annual costs associated with current asthma to € 352 million in the entire Danish population aged 20-44. Conclusions: The economic burden of asthma in Denmark is substantial and primarily due to productivity costs accounting for three quarters of the total costs.

Health-related quality of life (HRQL) is an important outcome measure in patients with respiratory diseases. This study aims at investigating HRQL in different respiratory disorders. Controls and cases of COPD, current asthma, past asthma, non-allergic rhinitis, allergic rhinitis and "Other Respiratory Conditions" (ORC) were compared. SF-12 median score ranged from 49.4 (95%CI 47.6-51.2) for COPD cases to 53.0 (95%CI 52.5-53.9) for current asthma cases and MCS score from 47.9 (95%CI 44.3-51.5) for COPD cases to 49.9 (95%CI 48.6-51.2) for current asthma cases (Tab1).

Table 1: Adjusted median (95%CI) and statistical significance of PCS and MCS scores in respiratory disease cases compared to controls

<table>
<thead>
<tr>
<th>PCS</th>
<th>Median (95%CI)</th>
<th>p-value (vs control)</th>
<th>MCS</th>
<th>Median (95%CI)</th>
<th>p-value (vs control)</th>
</tr>
</thead>
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<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Allergic rhinitis</td>
<td>54.2 (54.2-55.3)</td>
<td>0.005</td>
<td>45.6 (45.6-50.4)</td>
<td>0.003</td>
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<tr>
<td>Anergic rhinitis</td>
<td>54.3 (53.3-54.3)</td>
<td>0.005</td>
<td>45.3 (45.3-50.3)</td>
<td>0.003</td>
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</tr>
<tr>
<td>Other respiratory symptoms</td>
<td>53.8 (52.8-55.8)</td>
<td>0.003</td>
<td>45.7 (45.7-50.7)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Post asthma</td>
<td>53.8 (53.8-54.8)</td>
<td>0.003</td>
<td>45.5 (45.5-50.5)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Current asthma</td>
<td>50.2 (49.2-51.2)</td>
<td>0.009</td>
<td>46.5 (46.5-51.5)</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

To our knowledge, this is the first study to perform a direct and simultaneous comparison of quality of life in several respiratory disorders. Subjects who suffered from COPD, current asthma and ORC had poorer HRQL than controls.
P1771
Socioeconomic position and use of drugs in chronic obstructive pulmonary disease (COPD): A population-based cohort study in Rome, Italy
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Introduction: Little is known about “real-life” use of evidence-based recommended drugs in COPD. We tested the hypothesis that drug prescription vary according to socioeconomic position.

Methods: All people (55-64 years old) discharged in 2006-07 with a diagnosis of COPD exacerbation, resident in Rome (2,700,000 inhabitants) were selected from Hospital Information System (standardized ICD-9-CM coding). Drugs were retrieved from the regional drug prescription registry based on ATC codes (12-months follow-up after discharge). An area-based (census block) socioeconomic position (SEP) index was used for each patient (quintiles: I well off, V disadvantaged). Logistic regression was performed to take into account gender, age and comorbidities.

Results: 779 individuals were studied (mean age 58.1, 58% men). 55% were in the lower SEP levels. Disadvantaged people were more likely to have respiratory failure, diabetes, ischemic heart disease and heart failure. Proportions of people with at least two prescriptions during 12 months after discharge were: long-acting inhalants 70%, short-term inhalants 45%, xanthis 23%. No statistically difference was observed across SEP groups for long-acting (ORs ≥ 1.20, 95% IC=0.67-2.16) or short-acting inhalants (ORs≤1.55, 95% IC=0.90-2.68), while xanthis were more frequently prescribed for low SEP people (SEP-V vs. SEP-I OR=2.17, 95% IC=1.03-4.57; p trend < 0.05).

Conclusions: Disadvantaged COPD patients seem more exposed to xanthis whose effectiveness is less in comparison to inhalant drugs. We highlight the need for improving outpatient care programmes to reduce disparity in health.

P1772
Examination of multiple emergency inpatient admissions for asthma in England from hospital episode statistics (HES) 2005-2009
Rachel DaSantostefano1, Richard Baxter 2, Lianna Ishihara 2, Hana Muellerova2.

Objective: We described emergency asthma inpatient admissions in England from 2005-2009 and characterised factors associated with multiple asthma admissions.

Methods: This was a GSK-funded retrospective analysis (WEUSRTPS003) using HES1 industrialised data from England (©) 2010, re-used with permission). Patients with at least one emergency hospital admission where asthma was the primary diagnosis (ICD-10 J45, J46) on the first consultant episode within an admission were included. Using a backward elimination strategy, time to event modeling was employed to identify factors in the first asthma hospital record (length of stay [LOS], co-morbidities by ICD-10 chapter, gender) associated with a second asthma admission (occurring ≥3 days from first).

Results: There were 249,206 emergency admissions for asthma among 176,323 patients during the 4-year period. One-fifth of patients experienced ≥1 admission for asthma, where multiple admissions decreased with increasing age (27% age <18; 16% age ≥65); Median time to second admission was 6–7 months for each age group (<18, 18–44, 45+). Among adults, factors significantly associated with the second asthma hospital admission (p<0.05) included LOS ≥4 days (first admission), being female and co-morbidities (endocrine/metabolic, mental/behavioral, nervous system, circulatory).

Conclusions: The burden of asthma exacerbation requiring hospitalisation in England is substantial; one-fifth of patients admitted for asthma experienced multiple admissions (2005-2009). Co-morbidities were associated with a second admission for asthma in adults, suggesting that other health conditions may contribute to asthma morbidity.

223. Models of disease and drug actions

P1773
Inhaled budesonide induces corticosteroid-dependent gene expression in asthmatics: Validation in primary epithelial and airways smooth muscle cells
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Rationale: Inhaled corticosteroids (ICS) reduce inflammatory gene expression. This is usually attributed to direct inhibition of inflammatory gene transcription by the glucocorticoid receptor. However, while corticosteroids induce anti-inflammatory gene expression in vitro, this has not been examined in asthmatic subjects taking ICS.

Methods: Bronchial biopsies from atopic asthmatics taking inhaled budesonide (2×0.200 µg, twice daily for 11 days) or placebo were subjected to gene expression analysis using real-time reverse transcriptase-polymerase chain reaction. mRNA expression for the corticosteroid-inducible genes; TSC22D3 (GILZ), DUSP1 (MKP-1), both anti-inflammatory effectors, and FKBP5 (FKBP51), a regulator of glucocorticoid receptor function, was assessed. Cultured pulmonary epithelial and airways smooth muscle cells were also treated with corticosteroids before gene expression analysis.

Results: Expression of GILZ and FKBP51 were significantly elevated in budesonide-treated subjects compared to placebo. Budesonide also increased GILZ expression in cultured epithelial and smooth muscle cells and immunostaining showed GILZ expression in the airways epithelium and smooth muscle of asthmatic subjects.

Conclusions: Expression of corticosteroid-induced genes, including the anti-inflammatory gene, GILZ, is upregulated in the airways of asthmatic subjects taking medium daily doses of inhaled budesonide. The biological effects of such regulation need to be considered when assessing ICS action. Funded by AstraZeneca.

306s
P1776 Effects of beclomethasone dipropionate and formoterol in reducing oxidative stress induced by cigarette smoke extracts and IL-17
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Rationale: Oxidative stress is involved in airway inflammatory diseases. Inhaled corticosteroids reduce airway inflammation and the combination with long-acting β2 agonists enhances this effect.

Objective: To investigate whether cigarette smoke extracts (CSE) and interleukin-17A (IL-17A) activate airway epithelial cells to release markers of oxidative/nitrosative stress and to investigate the effect of beclomethasone dipropionate (BDP) and formoterol.

Methods: Human bronchial epithelial cells (16HBE) were stimulated with different concentrations of CSE (from 0 to 10%) to evaluate the expression of IL-17 receptor (IL-17R). IL-17A was also added to evaluate the production of ROS and nitrite/nitrate (NOx). The effects of BDP (10−6M) and Formoterol (10−6M), alone and in combination, were evaluated.

Results: CSE increased the expression of IL-17R in 16HBE in a dose-dependent manner with a maximum effect at 2.5% concentration (p<0.001). Both CSE and IL-17A separately increased the production of ROS and NOx (p<0.05) and their combination synergistically further increased the production of these markers (p<0.001). BDP alone was able to completely restore the baseline values in terms of IL-17R expression (p<0.001) and its combination with Formoterol was superior in reducing the ROS and Nitrite/Nitrate production (p<0.001).

Conclusions: Cigarette smoke and IL-17A increase the production of oxidative/nitrosative markers in human bronchial epithelial cells, this effect being reduced by BDP either alone or combined with Formoterol. Funded by: Chiesi Farmaceutici, S.p.A.

P1777 Activated protein phosphatase PP2A by formoterol enhances nuclear translocation of glucocorticoid receptor induced by budesonide
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Introduction: We have reported that formoterol (FM), a long-acting β2-adrenoceptor agonist, restores corticosteroid (CS) sensitivity by activation of a serine/threonine protein phosphatase PP2A (ERJ 2009;34:583s). However, the molecular mechanisms that FM activates PP2A and restores CS sensitivity have not been elucidated.

Aims: To investigate the mechanism of PP2A activation by FM and the involvement of PP2A in glucocorticoid receptor (GR) nuclear translocation induced by CS budesonide (BUD).

Methods: Phosphate activation of immunopurified PP2A from U937 monocytic cells was measured by fluorescence-based assay. A549 lung epithelial cells, without functional β2-adrenoceptor, were used as control cells. Direct effect of FM was evaluated using PP2A immunopurified from cell membrane and recombiant PP2A. FM and GR ratios under PP2A inhibition by okadaic acid (OA) or overexpression were determined by western-blot.

Results: FM enhanced PP2A activity in both U937 and A549 cells and the effects were not blocked by a β2-adrenoceptor inhibitor (ICI-185551). FM directly activated PP2A-immunoprecipitates in the membrane and recombiant PP2A. PP2A was detected in GR-immunoprecipitates. PP2A inactivation by OA reduced GR nuclear translocation by BUD and abrogated FM-mediated increase of GR translocation while PP2A overexpression enhanced BUD-induced GR translocation and further increased enhancement of GR translocation by FM.

Conclusions: FM directly activates PP2A in β2-adrenoceptor-independent manner. PP2A associated with GR enhances GR nuclear translocation by BUD. This mechanism may contribute to the clinical benefits of BUD+FM combination therapy.

P1778 Effect of fluticasone and formoterol combination therapy on airway remodeling
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Background: Macrophage infiltration, thickening of the basement membrane and increased mass of airway smooth muscle influence asthma airway remodeling.

Different cell types contribute to extracellular matrix deposition. Airway smooth muscle cells (ASM) not only contract but also proliferate, respond to inflammatory stimuli and produce extracellular matrix. As shown previously, glucocorticoids increase the deposition of extracellular matrix by human ASM under inflammatory conditions.

Methods: To analyse the effect of the β2-agonist formoterol on glucocorticoid-induced extracellular matrix deposition, primary ASM cultures were set up from asthmatics and non-asthmatic controls. Confluent cells were stimulated with 5% serum with or without a single drug or a combination for a further 72 hr with B3H proline (0.5μCi/μl). Total extracellular matrix and collagen deposition were monitored by scintillation counts, described earlier.

Results: Compared to non-stimulated cells 5% serum increased matrix and collagen deposition by +22% which was further increased in the presence of 10-8 M glucocorticoids (dexamethasone: +86%, budesonide: +66%, beclomethasone: +59%, fluticasone: +55%). However, 10-8 M formoterol restored serum-induced matrix and collagen deposition by 36%. In combination, formoterol abolished the stimulating effect of glucocorticoids on matrix and collagen deposition and reduced matrix deposition. This was dose-dependent.

Conclusions: Our data show that β2-agonists combined with glucocorticoids reduce the excessive matrix deposition induced by glucocorticoids alone. Thus, combination therapy may exhibit benefits for asthmatic patients beyond bronchodilating and anti-inflammatory effects.

P1779 AZD3199: A potent and selective β2-adrenergic receptor agonist with rapid onset of action
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Background: β2-agonists are standard treatments for asthma and COPD and are variingly optimized for a number of key pharmacological properties, such as receptor selectivity, systemic exposure, onset of action and duration of effect. AZD3199 is a novel ultra long acting β2-agonist (uLABA) with improved properties designed to combine 24 hour duration of effect with low systemic exposure and an onset of action similar to that of formoterol.

Methods: The affinity, potency and efficacy of AZD3199 were measured at human β2-adrenergic receptors. Onset of action was measured as relaxation of constricted guinea pig trachea and human bronchial tissue. Activity at the hERG voltage-dependent potassium channel was determined using electrophysiology. Plasma protein binding was measured in multiple species.

Results: AZD3199 was a potent agonist (6 nM EC50) at the human β2 receptor with an intrinsic activity of 0.8 relative to formoterol. AZD3199 had a rapid onset of action in both guinea pig (22 min) and human (11 min) lung tissue, very similar to formoterol (G-Pg 23 min, human 13 min) and significantly faster than salmeterol (>100 min in both). Similar β2-agonist activity was seen across multiple species including guinea pig, rat, dog, mouse and rabbit. AZD3199 was highly selective (>1500 fold affinity) for the human β2 receptor over human β1 and β3 receptors with no agonism at either receptor. No activity was seen at the hERG channel at concentrations up to 2μM. High plasma protein binding (>90%) was seen across multiple species offering the potential for reduced systemic exposure.

Conclusion: AZD3199 is a potent and selective uLABA with an onset of action similar to that of formoterol.

P1780 Oxidative stress-induced corticosteroid insensitivity is reversed by formoterol via inhibition of PI3K signalling in peripheral blood mononuclear cells from patients with COPD and severe asthma
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Rationale: COPD patients show a poor response to corticosteroids which has been linked to oxidative stress. Here we show that the long-acting β2-agonist formoterol (FM) reversed corticosteroid insensitivity after oxidative stress via inhibition of phosphoinositide-3-kinase (PI3K) signalling.

Methods: The responsiveness to corticosteroids dexamethasone (DEX), budesonide (BD) and salmeterol (SM) was measured in PBMCs from patients with COPD or severe asthma.

Results: PBMCs from patients with severe asthma and COPD are less sensitive to DEX compared to healthy volunteers. Although both BM (10−7M) and salmeterol (5M, 10−7M) reversed DEX insensitivity in PBMCs of severe asthma, only FM shows this effect in COPD. In U937 cells, exposure to H2O2 decreased BUD and FP sensitivity and increased Akt phosphorylation as a footprint of PI3K activation. FM restored sensitivity to BUD and FP while the effects of SM were weaker and not statistically significant, and FM but not SM, partially inhibited H2O2-induced Akt phosphorylation. H2O2 also decreased SM-induced cAMP production in U937 cells but did not affect the response to FM. The reduction of SM effects by H2O2 was reversed by pretreatment with a PI3K inhibitor.

Conclusion: These results suggest that FM restored corticosteroid sensitivity via inhibition of PI3K signalling and that a combination of a corticosteroid with FM may be more effective than that with SM in conditions of high oxidative stress, such as in COPD. Funded by AstraZeneca
P1781
Endogenous PGE2 contributes to antigen-induced contractions of guinea pig trachea
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We have previously shown that PGE2 via EP3 receptors maintains basal tone of guinea pig trachea (GPT). Our aim was to assess if antagonism of PGE2 also affected antigen-induced contractions.

Isometric responses to administration of ovalbumin (OVA) were recorded in GPT from guinea pigs sensitized to OVA and expressed as % of the maximal contraction to histamine 100μM. Before challenge with OVA, the selective EP3 antagonist, ONO-8130; 10(nM) antagonist was given to naïve preparations as well as together with different combinations of inhibitors and antagonists of histamine (mepyramine and metiamide), leukotrienes (zileuton) and prostaglandins (indomethacin).

As shown previously, inhibition of one or two mediator classes, generally, had no significant effects, whereas triple mediator antagonist (antihistamines+zileuton-indomethacin) abolished the response to OVA challenge. However, EP3 antagonist partly reduced the antigen contraction. Moreover, when the EP3 antagonist was given together with antihistamines and zileuton, the response to OVA was abolished (Table 1).

Table 1. Contraction (% max) to highest OV A dose

Control | 75±5  
M & M | 72±7  
INDO | 84±5  
ONO | 59±4*  
ZIL | 77±1  
INDO + M & M | 83±1  
ONO + M & M | 59±10  
ZIL + M & M | 65±7  
ZIL + M & M + INDO | 5±3*  
ZIL + M & M + ONO | 6±3*  

*p<0.05 vs control, *p<0.05 vs ZIL + M & M

Effect of indomethacin together with antihistamines and anti-leukotrienes confirms that proteinoids mediate part of the antigen-induced contraction. The new finding is that EP3 antagonism mimics the effect of indomethacin. This suggests that PGE2 is the main proteinoid mediating the antigen-induced contractions of GPT, a preparation that is known to respond similarly to human airways where the effects of PGE2 still await complete delineation.

P1782
Flumoxeme propionate inhaled 3 hours after an early allergen reaction partially inhibits the late phase reaction
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Introduction: Inhalation of 800μg budesonide (AERJACM 1994;149;1447) or 500μg beclomethasone (JACI 1995;91;1163) upon resolution of the allergen-induced early phase response inhibits the late phase asthmatic response (LAR) by 39% and 70%, respectively. This has never been tested for the highly lipophilic corticosteroid Budesonide propionate (FP).

Methods: This randomized double-blinded, placebo-controlled, 3-way crossover study (NCT00716693) was conducted in 6, mild allergic asthmatic patients with a documented dual bronchoconstrictor responses to inhaled allergen. Patients underwent 3 allergen challenges separated by 14 day washout periods. Patients inhaled placebo, 250μg or 1000μg FP at 3 h after allergen challenge, and the magnitude of the LAR was measured at regular intervals until 7 h post challenge. Sputum induction was performed before, 7 h and 24 h post challenge, and methacholine PC20 measured before and 24 h post challenge.

Results: Five patients completed the study. 250μg and 1000μg FP significantly attenuated the LAR compared to placebo: the mean (SD) maximum/6% fall in FV31 during the late response was 25.2% (6.2) with placebo, 15.1% (7.1) with 250μg FP (p<0.01), and 18.3% (8.2) with 1000μg FP (p=0.04). Inhibition of the LAR was 40% and 27% for 250μg and 1000μg FP, respectively. There was no effect of FP on allergen-induced sputum eosinophils, with a trend for reduced AHR which went 3 allergen challenges separated by 14 day washout periods. Patients inhaled placebo, 250μg and 1000μg FP significantly.

Conclusion: FP on allergen-induced sputum eosinophils, with a trend for reduced AHR which went 3 allergen challenges separated by 14 day washout periods. Patients inhaled placebo, 250μg and 1000μg FP significantly.

P1783
Effect of olodaterol on the relaxation of small airways
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Olodaterol (Ol) is a novel, selective, β2-agonist which offers bronchoprotection in mild asthmatics with duration of action of at least 24h. Small airways are the major site of obstruction in patients with COPD. Thus novel bronchodilators that act on the small airways may be of benefit for COPD. Therefore, this study compared the effect of Ol and formoterol (Fm) on human and rat small airways.

Precision cut lung slices (PCLS) were obtained from rat lungs and human lung tissue obtained following resection. Videomicroscopy was used to measure small airway relaxation.

Rat small airways were contracted to increasing concentrations of carbachol (EC50=0.11±0.04μg/M, n=6). Carbachol contraction was then repeated on the same airways following pre-treatment with PCLS with Ol or Fm (1μM). Both agonists significantly (p<0.05) inhibited carbachol-induced contraction (Ol: EC50=0.15±0.5μg/M and Fm: 0.34±0.07μg/M, n=6). Carbachol contracted human small airways with an EC50 of 0.08±0.03μg/M (n=6) which was significantly inhibited (p<0.05) following pre-treatment with inbm Ol (EC50=0.7±0.3μg/M, n=6) and inbm Fm (EC50=1.0±0.6μg/M, n=6).

Following pre-contraction of rat small airways with 0.1μM carbachol both β2-agonists induced relaxation ~45% of maximal contraction (n=6). By contrast, carbachol-induced pre-contraction of human small airways was completely reversed by both agonists with EC50 values of 4.3±5.7μm (n=6) and 46.1±37.9μm (n=6) for Ol and Fm respectively (P<0.005).

Ol and Fm had significant bronchodilatory effects on rat and human small airways. Ol was comparable to Fm and showed significantly increased relaxation following partial pre-contraction of human small airways to carbachol.
P1786
Neutralizingants of CXC12: Anti-inflammatorystimulanteffect onan allergicmodel of asthma
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Introduction: The chemokine CXCL12plays an important role in inflammation. Our team identified a small molecule neutralizing CXCL12, belonging to the family of chalcone, named C05. C05 inhibits interaction with its receptors, CXCR4 and CXCR7 (Hachet-Haas et al, JBC 283:23198,2008), and the eosinophil infiltration in a mouse model of allergic eosinophilic airway inflammation. We here evaluated the effect of this neutralizing C05 on airway hyperresponsiveness (AHR), inflammation and airway remodelling.

Methods: Nine week-old male Balb/c mice were sensitized to ovalbumin (OVA/Alum i.p, D0, D7) and challenged to OVA or solvent i.n. on D18,19,20,21, C05 (350µmol/kg, iv vehicle was administered i.p. once daily, 2h before each OVA challenge.

Results: C05 induced AHR (whole body plethysmography), eosinophilia, increase in IL-4, IL-5 and mucus secretion in bronchoalveolar lavage fluid, increase in lung collagen, as well as increased IgE and IgG1 in plasma. C05 decreased AHR (44±2%), eosinophilia (48±7%), IL-5 (44±8%), mucus (67±10%) in BAL, and lung collagen (100±21%). IgE and IgG1 levels in plasma and IL-4 secretion in BAL were not modified. In addition, C05 did not modify body or spleen weight. Furthermore, C05 did not induce any CXCR4+ cell recruitment in blood as opposed to AMB3100, a CXCR4 antagonist vs control group (11.4±3, 30.3±9, 9±1%).

Conclusion: The CXCL12 neutralizing therefore appears as a safe and good candidate in this asthma model.

P1787
Anti-inflammatory effects of garenoxacin on IL-8 production and ERK1/2 activation induced by lipopolysaccharides in A549 and THP-1 cells
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Objective: The anti-inflammatory properties of macrolides have been applied to the treatment of inflammatory airway diseases. Although the anti-inflammatory properties of garenoxacin have been reported, no reports are available regarding a newly developed fluoroquinolone, garenoxacin (GRNX). To examine the immunomodulatory effect of GRNX, we examined the transcription and secretion of inflammatory cytokines by human airway epithelial cells and monocytes stimulated with lipopolysaccharide (LPS).

Methods: A human lung epithelial cell line (A549) and a human monocye cell line (THP-1) were stimulated with LPS and exposed to different concentrations of GRNX. The transcription of interleukin 8 (IL-8) at 3 h was measured in cell lysates using real-time PCR. The secretion of IL-8 was measured in the supernatants of the cell cultures at 24 h (A549 cells) or 9 h (THP-1 cells) using an enzyme-linked immunosorbent assay.

Results: LPS stimulation resulted in a significant increase in the transcription and secretion of IL-8 by A549 and THP-1 cells. Treatment with GRNX significantly inhibited the transcription and secretion of IL-8 by LPS-stimulated cells through inhibition of LPS-induced ERK1/2 phosphorylation.

Conclusions: GRNX has an anti-inflammatory activity through its capacity to alter the secretion of IL-8 from A549 and THP-1 cell lines.

P1788
Polymerized type I collagen reverts airway hyperresponsiveness development in a guinea pig asthma model
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Recently, polymerized type I collagen (PoC) has been shown to display anti-inflammatory and anti-fibrotic properties in an asthma model. The effect of PoC in the pathobiology of asthma is unknown. Our aim was to study the effects of PoC in airway obstruction and responsiveness in a guinea pig model of allergic asthma with remodelled airways. After an initial sensitization protocol, guinea pigs were intermittently exposed to allergen (ovalbumin, OA) applied every 10 days for up to 125 days (asthma model group), receiving a total of 12 OA challenges. The control group received saline solution instead of OA. Some animals from both asthma model and control groups were treated with 0.66 mg/ml PoC aerosols administered every 5 days from day 65 to 120. Airway responsiveness to histamine was evaluated before the first OA challenge and at the sixth and twelfth OA challenges. From the first challenge on, OA induced a transient airway obstruction and a progressive rise in baseline Penh (a broncho-obstruction index), measured by barometric plethysmography, which was not modified by PoC treatments. At the sixth challenge, OA-induced hyperresponsiveness was abolished at twelfth OA challenge by PoC treatment. In a separate guinea pig group euthanized at the sixth OA challenge, airway subepithelial fibrosis (determined by morphometry) and granulocyte infiltration were observed. PoC treatment reduced both, granulocyte and fibrosis observed at the twelfth challenge. Our data suggest that the rise of Penh baseline is not induced by airway fibrosis, and that PoC is a biomarker which might become a pharmacological tool to reduce fibrosis, inflammation and hyperresponsiveness in asthma.

P1798
Reduces inflammatory parameters in airways of diabetic-antigen sensitized guinea pigs
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It is well established that there is a negative association between asthma and type 1 diabetes and relative lack of insulin in an organism results in an overall reduction in inflammatory reactions. This study was planned to determine the inflammatory events in antigen sensitized diabetic guinea pigs. Twenty-five male guinea pigs were categorized into five groups of five each as follows: diabetic, antigen sensitized, diabetic-antigen sensitized, insulin-treated diabetic-antigen sensitized and control animals. Induction of experimental diabetes and antigen sensitization were performed by injection of streptozotocin and ovalbumine, respectively. Animals were killed by exsanguination and bronchoalveolar lavage (BAL) was performed. BAL fluid cellular and protein contents were determined. Airway responsiveness to acetylcysteine was assessed. Histopathological examinations were performed on the lungs. Decreases in the airway reactivity in diabetic-antigen sensitized animals were found compared to antigen sensitized animals. Experimental diabetes decreased antigen-induced protein leakage into the airspace as well as the accumulation of inflammatory cells in BAL fluid of antigen sensitized animals. Histopathological results showed that conduction of experimental diabetes significantly reduced the number of eosinophils in the lungs of antigen sensitized animals. Treatment with insulin completely reversed all mentioned results in the antigen sensitized diabetic animals. Experimental diabetes causes were found to decrease the airway reactivity and inflammatory responsiveness induced by antigen sensitization due to a reduction in the insulin levels.

P1799
Pharmacological assessment of the effects of SB-705498 on capsaicin-induced responses in healthy volunteers and patients with non-allergic rhinitis
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Rationale: "Nasal hyper-responsiveness" has been proposed as a key mechanism driving nasal symptoms in patients with non-allergic rhinitis (NAR). Here, we explore the potential clinical use of the selective TRPV1 antagonist, SB-705498, for treatment of symptoms of rhinitis.

Methods: Two clinical studies were here conducted to assess the effect of SB-705498 on nasal responses to incrementally dosed, unilateral intranasal capsaicin challenge: In the first study, a single 400µg oral dose of SB-705498 was assessed in healthy volunteers (HVT). In the second study, 12mg of SB-705498 was administered to topically patients to non-allergic rhinitis (SB-705498 or placebo was administered according to a randomised, double blind, crossover (HVT)) or parallel group (NAR) design. 1 hour post dosing, incremental capsaicin challenge (2.5, 12.5 and 50µg) was performed. Symptom scores, secretion weights, peak nasal inspiratory flow (PNIF) and mediators in nasal secretions were evaluated. Blood samples were collected for pharmacokinetic analysis.

Results: Both studies showed a clear signal for effect of SB-705498 versus placebo on the clinical endpoints following intranasal challenge with capsaicin. The relative dose potency for TSS was 3.33 (1.45, 8.26 95% CI) in HVT and 2.81 (0.78, 10.7 95% CI) in NAR patients. All other clinical endpoints (satisfying parallelism) showed approximately 2-5 fold potency shift, except PNIF in NAR patients.

Conclusion: SB-705498 inhibits capsaicin induced nasal responses in HVT and NAR. SB-705498 has potential for further development as a novel, topical intranasal medicine for treatment of rhinitis.
P1794

Cost-effectiveness of a lung health intervention in US smokers
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Objective: to determine smoking cessation ward rounds increase referrals to smoking cessation services? A survey in a UK district general hospital

Aims: To prove that NRT in ICU patients decreases the use of sedatives and analgesics, the number of days on ventilator, and the total ICU stay.

Methods: The study was performed in the 20 bed ICU. Forty patients meeting inclusion and exclusion criteria were randomized into either an interventional or control group. Patients in the interventional group received a 21mg nicotine patch every day until the patient was discharged from the ICU, transferred to the general medical floor, or until 10 weeks. Patients in the control arm received fake patch. The use of sedatives and analgesics during ICU stay, and use and duration of invasive mechanical ventilator were noted. The length of ICU stay was also compared in both the groups.

Results: Twenty-seven patients were male,13 were female. The mean age of the interventional group patients was 57.4 years and 52.5 years in the control group. The mean APACHE II score was 14.3 in the interventional group vs. 13.8 in the control group. The mean length of ICU stay in the interventional group was 4.5 days while in the control group mean length of ICU stay was 7 days. The mean number of days on ventilator in interventional group was 1.9 days vs. 3.5 days in the control group. The number of days on sedation and analgesia was also less in the interventional group compared to the control group.

Conclusion: The length of ICU stay and the number of days on ventilator decreases in the patients receiving NRT.

P1795

High and low intensity interventions for smoking cessation during pregnancy, an RCT

Aims and objectives: The aim of this RCT is to test whether offering pregnant smokers a high intensity intervention for smoking cessation increases the rate of smoking cessation and, in comparison to a usual care low intensity intervention.

Methods: The high intensity intervention (n=24) included: 30 minutes of cognitive-
behavioural intervention and a self-help manual. The control group (n=30) received 5 minutes of low intensity intervention. Smoking cessation was biochemically validated by urine cotinine samples both at the baseline and around the 32nd week of gestation among both groups (ClinicalTrials.gov Identifier: NCT01210118).

Results: The preliminary results indicate a significantly higher percentage of pregnant smokers quit smoking in the experimental group (20.8%) than in the control group (6.7%). Urine cotinine levels ranges were similar in both groups before the intervention. A significant decrease in urine cotinine concentrations after the intervention, were noted among both groups with the participants of the experimental group found to have a larger decrease in cotinine concentrations (_ctl 0.026±0.63 ng/ml vs. experimental group 40±1.19 ng/ml).

Conclusions: These preliminary results indicate that a high intensity intervention was found more effective than a low intensity intervention for smoking cessation during pregnancy, indicating its possible usefulness within clinical practice.

P1796 Predicted impact of access to varenicline on abstinence simulating multiple quit attempts over smokers’ lifetimes


Background: Relapse to smoking is a common challenge to many quitters, thus, access to effective smoking cessation treatment (SCT) for multiple quit attempts may be important in achieving permanent abstinence.

Objective: To evaluate the impact of access of Varenicline (V) vs. no-access to varenicline (\( V^-\)) on predicted health benefits and costs over smokers’ lifetimes.

Methods: A discrete event simulation of SCT allowing multiple quit attempts (QA) with choice of treatments predicting response and possible relapse, as well as estimates of lifetime health and economic outcomes in a U.S. population was implemented. The simulations compare outcomes of smokers who had access to varenicline for all QA’s with those without any access to varenicline. Smokers could also use NRT, bupropion, behavioral modification, or “cold turkey” for any QA, regardless of access to varenicline.

Results: The average predicted total abstinence time (tAT) is 113 months with \( V^-\) and 126 months with \( V^+\). The corresponding average lifetime QAs/smoker are 9.0 with \( V^-\) and 7.5 with \( V^+\). The percent of individuals achieving predicted abstinence is (at least 2 years by the time of analysis) is %68% with \( V^+\) and %72% with \( V^-\). For each simulated combitody (COPD, lung cancer, coronary heart disease and stroke), the incidence of new cases is lower with \( V^+\). Access to varenicline is dominant, i.e. more effective and less costly than no-access across all comparisons.

Conclusion: Providing access to varenicline over smokers’ lifetimes results in better health outcomes at lower costs.

P1797 Smoking and treatments among asthma patients in South Korea

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Background: The prevalence of smoking in South Korea is high, an estimated 23.3% for adults. Studies have shown that active smoking impacts asthma morbidity and treatment response. However, little is known about the asthma therapies and treatments among asthma patients in South Korea.

Methods: A cross-sectional survey was conducted from Aug 2010–Jan 2011 at 16 urban hospitals in South Korea. Information on smoking status, asthma medications and exacerbations in the prior year was collected for consecutive asthma patients aged 18-60 yrs presenting for medical care.

Results: A total of 1347 asthma patients were included. Mean age was 43 yrs, 46% were male, 63% never smoked (NS), 16% were former smokers (FS) and 21% were current smokers (CS). The proportion of patients with ≥1 exacerbation in the prior year was 42% for NS, 38% for FS and 40% for CS (chi-squared p=0.52). Most patients were using ICS-LABA (73%) with no differences in use between smoking categories (72% of NS, 75% of FS and 76% of CS; p=0.40). Use of leukotriene modifiers (52%) was also common, with no differences in use between smoking categories (52%, 54% and 49% for NS, FS and CS, respectively; p=0.56). Twelve percent of patients were reported as using an ICS and there were slight differences in use between smoking categories (14%, 10% and 6% for NS, FS and CS, respectively; p=0.001).

Conclusion: The prevalence of smoking among this asthmatic patient population was similar to previously reported national rates in South Korea. Smoking status does not appear to affect the use of two common asthma medications; however, smoking status may influence the use of ICS.
percentages of subjects having lower respiratory flows or OVD or RVD or lung hyperinflation. Compared to the ECG group, the ENS group includes significantly lower percentages of subjects having lower respiratory flows or OVD or lung hyperinflation. Cigarettes and narghile smoking accelerate lung ageing with significantly higher estimated lung ages.

Conclusion: The plethysmographic profile of ENS is different from this of ECS and narghile smoking accelerates lung ageing.

P1800
The dynamics of free radical parameters in exhaled breath condensate (EBC) in smokers during the course of physical workload
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The aim of the study was to investigate the total nitrate/nitrites (TNN) and Fe^2+ concentrations in EBC in smokers compared with nonsmokers during the course of physical exercises.

Materials and methods: The study group included 30 smokers 20-23 y.o. with smoking history of 3-4 years. The control group consisted of 25 healthy (without any documented medical diagnosis) non-smokers 20-23 y.o. The TNN level in EBC was determined by nitrate reductor and Griess reagent, the concentration of Fe^2+ was observed by ferrozine method. All the data were determined in two points: baseline at rest and after exercise (when the heart rate was 100-120 beats per minute) in both groups.

Results: The results obtained demonstrated that there was significant decrease of TNN concentration in EBC in study group (the basal level of TNN in EBC was lower in 1.6 times compared with nonsmokers). During the course of physical exercises it was shown the increase of TNN level in EBC in smokers compared with nonsmokers (in 2.0 and 1.2 times respectively), also the increase of Fe^2+ basal concentration in lung tissue in 2 times compared with nonsmokers (p <0.05) was determined. During the exercise the Fe^2+ concentration in smokers was higher in 1.4 times as compared with nonsmokers (p <0.05).

Conclusion: The physical workload provide a significantly changes in free radical metabolism in smokers.

P1801
Time trends of smoking habits in Italy during the last decade
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Objective: To estimate time trends of smoking habits in Italy as a function of gender and occupation.

Methods: In the frame of the GEIRD study (Gene Environment Interactions in Respiratory Diseases) 10494 subjects, randomly selected from the general population aged 20-44 years in 7 Italian centres (Torino, Pavia, Verona, Sassari, Ancona, Terni, Salerno), answered a screening questionnaire between 2007 and 2010 (response percentage=57.2%). In 4 centres smoking prevalence was compared with prevalence recorded between 1998-2000 by the Italian Study of Asthma in Young (ISAYA).

Results: In the GEIRD study the prevalence of current smokers was higher in men (31.3%) than in women (24.2%), while the prevalence of past-smokers was similar (16.8% and 15.8% respectively). Current smoking was twice as prevalent among unemployed and blue collar (39%) as among managers and clerks (20-22%). In a multinomial model controlling for centre, sex, age, occupation, cumulative response percentage, season and type of response (postal/phone), the risk of current smoking largely declined from the first to the second survey (RRR=0.68, 95%CI 0.62-0.74). A significant, although smaller, decline was recorded also in the risk of being a past-smoker (RRR=0.85, 0.76-0.94). The declining trend did not differ by gender (time-sex interaction: P=0.206), but it was largely affected by occupation-time-occupation interaction: (P=0.004); it was particularly pronounced in managers, while being absent in unemployed.

Conclusion: Smoking prevalence has declined in this Italian population in both sexes. The declining trend, however, while pronounced in the highest socioeconomic classes, has not started yet among the lowest classes.
P1805 Maternal smoking during pregnancy and the risk of asthma related symptoms in the early childhood
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Maternal smoking during pregnancy and fetal growth retardation might adversely affect early lung development and increase the risks of asthma-related symptoms. The study of the associations of maternal smoking during pregnancy and fetal growth, measured in different periods of pregnancy with asthma-related symptoms in early childhood.

Methods: We performed a 4 years (2006-2010) prospective population-based cohort study starting in pregnancy. Fetal growth retardation was defined as a decrease of 1 gestational age adjusted standard deviation score in weight from 3rd trimester to birth. Maternal smoking during pregnancy (I, II, III trimesters) and wheezing, lower respiratory tract infections (LRTI) and diagnosed asthma until the age of 3 years were assessed by questionnaires. Adjusted logistic regression analyses were performed in 1217 subjects.

Results: Maternal first trimester only smoking was not associated with asthma-related symptoms in the children. Continued maternal smoking during pregnancy was associated with wheezing at 1, 2 and 3 years with adjusted odds ratios (aOR) 1.47 (94% confidence interval 1.14 to 19.4), 1.51 (1.13, 2.01) and 1.60 (1.09, 2.37), and with LRTI at 2 years (aOR 1.69 (1.19, 2.41)) but not with diagnosed asthma. Fetal growth retardation was not associated with any asthma-related symptoms. Children of continued smoking mothers with fetal growth retardation had higher risks of wheezing than children of smoking mothers without fetal growth retardation.

Conclusions: Continued maternal smoking during pregnancy is associated with increased risks of wheezing in early childhood. These associations are stronger in children with fetal growth retardation.

P1806 Second hand smoke exposure among hospital staff in Budapest, Hungary: A case study
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Background: The aim of the study was to assess the second hand smoke exposure levels in the wards of a public hospital.

Methods: An indoor air quality monitoring study was performed in hospital ward rooms. The measurements were performed with TSI SidePak AM510 Personal Aerosol Monitor in Budapest, Hungary.

Results: Mean PM2.5 levels in the wards of the hospital were 182.9 ± 135.6 μg/m3, in the clinical departments and health care workers’ rooms the mean was 191.5 ± 167.2 μg/m3. The highest levels of indoor air pollution were found in the laboratory (336 μg/m3), intensive care unit (230 μg/m3) and neonatology (163 μg/m3).

Conclusions: The results of our study indicate that there is a need for public health action and implementing smoking-free policies in the hospital in order to reduce second hand smoke exposure.

P1807 The influence of early exposure to tobacco smoke for pulmonary disease
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Background: Smoking is a very serious problem for COPD, lung cancer and other chronic pulmonary diseases. However, there are few studies on early exposure to tobacco smoke. Smoking rate in Japan decreased to 21.8%. However it is still higher in the northern area (Hokkaido). In particular, it is 31.0% in Erimo town (southernmost extreme of Hokkaido), which is higher than that of any other cities in Hokkaido. The reason is that when parents smoked, the child set fire to tobacco and handed it as a custom in 1940’s. Because a hand was wet while fishing, they were not able to set fire themselves.

Aim: We evaluated the influence of early exposure to tobacco smoke on prevalence of COPD and lung cancer.

Methods: Using the results of the medical checkup carried out at the Erimo town health division and the Town clinic, we analyzed about 6000 residents’ epidemiologic data.

Results: Majority of residents were found exposed to tobacco smoke actively or passively from a young age. Housemate smoking rate was 81.0%. The mortality of chronic respiratory disease was 71.4 per 100,000 person-years that was far exceeded from the national average (11.4 per 100,000 person-years). COPD prevalence (465.5 per 100,000 person-years) was significantly higher than the national average (136.2 per 100,000 person-years). Lung cancer prevalence was also very high (87.2 per 100,000 person-years).

Conclusion: Early exposure to tobacco smoke in childhood significantly increases prevalence of COPD and lung cancer. In Japan, young generation showed still high smoking rates (14.3% aged 20s, 18.0% aged 30s). Smoking cessation is the most important intervention to prevent disease progression.

P1808 Determination of cutoff points for smoking biological markers and the influence of involuntary smoking exposure
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Background: The reference values used for smoking biological markers should be determined in each country or region because there are many factors that can influence them.

Objective: To estimate the cutoff points of exhaled carbon monoxide (ECO), carboxyhemoglobin (COHb), plasma cotinine and urinary cotinine in order to differentiate active smokers from never-smokers.

Methods: In a cross-sectional study with 53 active smokers (30 males) and 49 non-smokers (14 females), ECO, COHb, plasma cotinine and urinary cotinine were measured.

Results: Anthropometric variables in both groups showed no statistically significant differences (p-value>0.05).

Active smokers had significantly higher levels of ECO, COHb, plasma cotinine and urinary cotinine than non-smokers (p-value<0.05).

It was determined the following cutoff points for biological markers: ECO - 4 ppm (sensitivity 100% and specificity 96.2%); COHb - 1.6% (sensitivity 100% and specificity 96.2%); plasma cotinine - 10 ng/mL (sensitivity 100% and specificity 94.3%); urinary cotinine - 779 ng/mL (sensitivity 100% and specificity 96.2%).

In the absence of smoking exposure, the cutoff point for urinary cotinine changed to 22 ng/mL.

Conclusion: All the biomarkers presented an excellent ability to discriminate between smokers and non-smokers.

225. Tuberculosis: from bench to bedside

P1809 T_{reg} cells are expanded among bronchoalveolar lymphocytes in healthy tuberculosis contacts with positive interferon-γ release assay responses
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Background: A positive Interferon-γ release assay (IGRA) after exposure to tuberculosis indicates a systemic immune response to Mycobacterium tuberculosis (MTB). However, most people will remain IGRA-negative (IGRA-) after exposure. In mice, regulatory T-lymphocytes (T_{reg}) can deter the pulmonary clearance in early infection, possibly preventing a systemic immune response.

Objective: To study the local immunity in TB-exposed health care workers without active disease.

Methods: FACs analysis on bronchoalveolar lavage (BAL) cells including T_{reg} cells (CD4+CD25+CD127-) and activated macrophages (HLA-DR+). Questionnaire for demographic, and health-related data. Blood IGRA.

Results: Demographic and epidemiological parameters were not statistically different. Of 10 IGRA- and 12 IGRA+ subjects, the BAL of the latter group showed a
To study the influence of CD4+ and CD8+ T-cell counts on IGRA results in HIV/AIDS patients.

Aim: To study the influence of CD4+ and CD8+ T-cell counts on IGRA results in HIV/AIDS patients.

Materials and methods: QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis, Melbourne, Australia) and T-SPOT.TB (SOT) (Oxford Immunotec, UK) tests were performed according to manufacturers' instructions. CD4+ and CD8+ T-cell counts were determined by flow cytometry (BD, FACSCanto II). Spearman correlation and t-test were used for statistical analysis. All pts provided written informed consent.

Results: From January 2010 to January 2011, 105 (62% males) (18-66 yrs) HIV-infected individuals in different stages of progression were recruited. The mean CD4+ and CD8+ cell counts was 448 cells/µl (74-3871) respectively. 24/105 pts were positive in both IGRA results with negative production did not correlate with absolute CD4+CD8+ T-cell counts (p<0.05). Mean values of CD4+CD8+ T cells in pts with indeterminate results were insignificantly lower than in pts with negative and positive results in both IGRA's (p<0.05).

Conclusions: Our data demonstrate that TB antigen-specific immune responses in HIV/AIDS pts with indeterminate results were insignificantly lower than in pts with negative and positive results in both IGRA's. The present work is devoted to relative research of some cy	olines (IL-1β, IL-8, IL-12, TNF-α) at the tuberculosis patients with the subsequent evaluation of their role in pathogenesis of various forms of pulmonary tuberculosis.

Materials and methods: The clinical and immunological inspection is executed at 193 patients with active pulmonary tuberculosis.

Results: At infiltrative tuberculosis the high level of production IL-1β and IL-8 was combined with the maximal stimulation index of IL-1β and TNF-α, but low stimulation index of IL-8. Production of IL-2 exceeded the patients with more disseminated forms of a tuberculosis - disseminated and caseous pneumonia. Fibro-cavernous tuberculosis was characterized by more intensive production of IL-2, low serum contents of IL-1β, TNF-α and lower activity of IL-8. The level of inflammatory cytokines production (IL-1β and TNF-α), alongside with a low index of their stimulation is characteristic for a disseminated tuberculosis, that testifies to a state of hyper activation of immunocompetent cells. In caseous pneumonia, alongside with the maximal reduced of IL-1β, TNF-α and IL-2, the highest index of stimulation IL-1β and TNF-α was marked.

Conclusion: The received data testify to the highest degree of an activation of cells of cytophagous in patients with infiltrative tuberculosis, and their expression depends on the caseous incompleness in caseous pneumonia. The down stroke of production not only IL-2, but also IL-1β alongside with a high level of IL-8, corresponds to the extremely serious state of the patients.

PI1801

Lethal tuberculosis in a previously healthy adult with IL-12 receptor deficiency

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Introduction: Most patients with disseminated tuberculosis (TB) have no known underlining immunodeficiency. Here, we report the first case of disseminated TB in an adult patient with underlying IL-12Rβ1 deficiency.

Case: A 38 year old man was admitted in hospital due to fever, generalized lymphadenopathy, and hepatosplenomegaly. He had a history of anti-TB treatment in the previous 3 years. Despite normal chest X-ray, sputum smear was positive for Acid-fast bacilli (AFB) and PCR was positive for Mycobacterium tuberculosis complex. Drug susceptibility test revealed multi-drug resistance (MDR) to INH and Rif. Standard MDR-TB treatment was initiated. Evaluation of immunologic and genetic status of patient revealed IL-12Rβ1 deficiency.

Despite initial response to treatment, the patient developed profuse diarrhea. In coloscopy, polypoid lesions were observed which were full of AFB. Linezolid and IFN-γ were added to the treatment but the patient passed away due to disseminated TB.

Conclusion: IL-12Rβ1 deficiency is a genetic etiology of severe TB in adults. We should consider genetic defects of the IL-12-IFN-γ circuit in adult patients with disseminated TB.
like sputum smears is time saving, simple and convenient compared with other culture based methods.

P1815

Genetic association studies between the MyD88 adaptor pathway SNPs and the development of tuberculosis

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Background: Tuberculosis (TB) is characterized by the formation of granulomas. Myeloid Differentiation factor (MyD)88 is the common adaptor molecule that communicates the Toll-like receptor (TLR) engagement on the cell surface to intracellular events. TLRs are extracellular receptors that recognize specific molecular patterns found in a broad range of microbial pathogens, triggering inflammatory responses. There is evidence that MyD88-/- animals fail to form granulomas, while animal studies indicate that MyD88 signalling pathway is crucial for the control of M.tuberculosis infection.

Objectives: We hypothesize that a defect in MyD88 pathway results in increased susceptibility of M. tuberculosis infection through reduced immune response following the recognition of the microorganisms by TLR proteins. To this end we analyzed SNPs in the MyD88 gene.

Methods: 93 TB patients with culture-proven or sputum-positive microscopy active TB and 92 controls were analyzed for the following SNPs: MyD88 -938C>A and MyD88 1944C>G.

Results: The MyD88-938CA genotype is associated with an increased risk of developing TB with an Odds Ratio (OR) of 2.62 (95% Confidence Intervals [CI] 1.35-5.22, p=0.006) while the MyD881944CC genotype is associated with an increased risk of developing TB (OR: 4.83 [95% CI]: 1.86-12.52, p=0.001).

Conclusions: The results indicate that the MyD88-938CA and the MyD881944CC genotypes may be associated with increased M tuberculosis infection susceptibility. Since the TB population has been in contact with M tuberculosis but only 10% of them will develop an active infection, our findings provide important insights regarding tuberculosis development.

P1816

NALP3 and CARD8 genetic polymorphisms and antibacterials-drugs induced hepatitis

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Backgrounds: Genetic susceptibility to the development of antibacterials drugs (ATD)-induced hepatitis is poorly understood yet. The NALP3 inflammasomes, which sense danger signals and produce IL-1β, may contribute to the initiation of inflammatory response and ATD-induced hepatitis. We examined if the polymorphisms in NALP3 inflammasome genes (NALP3 and CARD8) are associated with ATD-induced hepatitis.

Methods: We enrolled 80 patients with ATD-induced hepatitis and 238 ATD-tolerant patients. DNA was isolated from whole blood and genotyped for the single nucleotide polymorphisms (SNPs) in NLRP1 and CARD8. Genotype frequencies of SNPs and haplotypes were compared between patients with ATD-induced hepatitis and ATD-tolerant patients.

Results: OR seven SNPs of NALP3 (rs35829419, rs40612666, rs10754558, rs4353135, rs55466866, rs72653577 and rs10733113), there was no significant association with ATD-induced hepatitis. Analysis of NALP3 haplotypes found no significant relationship with ATD-induced hepatitis. C10X of CARD8 (rs2043221) was not associated with the risk of ATD-induced hepatitis.

Conclusions: These findings indicate that NALP3 and CARD8 genetic polymorphisms are not associated with the development of ATD-induced hepatitis in Korean population, and suggest that NALP3 inflammasome does not play important roles in the pathogenesis of ATD-induced hepatitis.

P1817

Mutations of the gyrA gene of mycobacterium tuberculosis leading to XDR tuberculosis in Kyrgyz Republic

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In the treatment of multidrug-resistant tuberculosis (MDR) the second line drugs are prescribed and among them the most ones are fluroquinolones. But the emergence problem of the recent years is the development of fluoroquinolone resistance or XDR tuberculosis. The XDR is associated with mutations in the gyrA gene which controls the proliferation of M.tb.

Aim: Analysis of mutations of the gyrA gene of M. tuberculosis (M.Tb) strains from patients of penitentiary system and civilian hospitals of Kyrgyz Republic.

Materials and methods: Sputum samples of 79 pulmonary tuberculosis (TB) patients were analyzed by biochip assay to detect the gyrA mutations of M.tb. From all samples the 33 sputum samples were taken from patients in the penitentiary system and 46 sputum samples were taken from patients in the civilian sector.

Results: M.tb resistant to fluoroquinolone were found in 8.7% of TB patients from the civilian sector and in 6% of TB patients from the penitentiary system which gives the resistance to fluoroquinolones of about 7.6% in general TB patients subpopulation. The detailed analysis of the mutations of gyrA gene revealed its location mainly in codons 90 and 94. The most frequent mutations was Asp94Gly (66.6%) but it was Ala90Val (16.6%). One case had the combination of both mutations Asp94Gly and Ala90Val.

Conclusion: In XDR tuberculosis patients from Kyrgyz Republic the resistance of M.tb to fluoroquinolones is mainly caused by Asp94Gly and Ala90Val mutations of gyrA gene.

P1818

Novel sequence-based assay for detection of pyrazinamide-resistant mycobacterium tuberculosis in clinical specimens from patients with pulmonary tuberculosis in Russia

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Pyrazinamide (PZA) is an important first-line antituberculous drug used in all regimens recommended by the WHO. However PZA susceptibility testing is not routinely performed in many laboratories so comprehensive surveillance studies of pyrazinamide resistance are rare. The aim of our study was to determine the occurrence of PZA-resistant M.tuberculosis. We developed the diagnostic kit based on direct sequencing of the gyrA gene that was expected to detect all type of mutations. We have examined 143 respiratory specimens obtained from 140 Russian patients with pulmonary tuberculosis. All patients have been classified into 5 groups depending on duration of treatment. The first group consists of patients with newly diagnosed tuberculosis who did not receive antituberculous drugs previously or only a few months ago. The second group included patients from 1 to 3 months of such treatment. PZA-resistance has been found in 9 (10.3%) cases from 87 patients of the first group. The frequency of PZA-resistance of patients from the second group has been amounted to 41.6%. In half of these cases we found heterogeneous populations of bacilli consisted of wild and mutation types. PZA-resistant strains were detected in 7 (36.8%) of 19 patients from the third group with a duration of treatment from 3 to 6 months, in 6 (75.0%) of 8 patients with a duration of treatment from 6 to 9 months, and in 4 (80.0%) of 5 patients receiving antituberculous drugs from 9 to 12 months. These data suggest that the sequencing assay may be useful for the direct and rapid detection of PZA-resistant M.tuberculosis in clinical specimens.

P1819

Results of spoligotyping of M. tuberculosis strains isolated in Belarus

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Introduction: Multidrug resistant tuberculosis (MDR-TB) is a severe threat to effective TB-control as well as to successful treatment of the individual patients. The reported incidence of MDR-TB in Belarus is somewhat lower than in its neighboring countries, but the level of MDR-TB causes severe obstacles for the national TB program.

Objective: To characterize MDR-TB and pan-susceptible M tuberculosis clinical isolates from TB patients in Belarus with a duration of treatment from 3 to 6 months, in 6 (75.0%) of 8 patients with a duration of treatment from 6 to 9 months, and in 4 (80.0%) of 5 patients receiving antituberculous drugs from 9 to 12 months. These data suggest that the sequencing assay may be useful for the direct and rapid detection of PZA-resistant M tuberculosis in clinical specimens.

Materials and methods: Sputum samples of 79 pulmonary tuberculosis (TB) patients were analyzed by biochip assay to detect the gyrA mutations of M.tb. From all samples the 33 sputum samples were taken from patients in the penitentiary system and 46 sputum samples were taken from patients in the civilian sector.

Results: M.tb resistant to fluoroquinolone were found in 8.7% of TB patients from the civilian sector and in 6% of TB patients from the penitentiary system which gives the resistance to fluoroquinolones of about 7.6% in general TB patients subpopulation. The detailed analysis of the mutations of gyrA gene revealed its location mainly in codons 90 and 94. The most frequent mutations was Asp94Gly (66.6%) but it was Ala90Val (16.6%). One case had the combination of both mutations Asp94Gly and Ala90Val.

Conclusion: In XDR tuberculosis patients from Kyrgyz Republic the resistance of M.tb to fluoroquinolones is mainly caused by Asp94Gly and Ala90Val mutations of gyrA gene.
P1820

Withdrawing

P1821

First experience with novel molecular diagnostic method for detection of M. tuberculosis and rifampicin resistance
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Latvia has middle level notification rate of tuberculosis (TB) and ranks among 27 countries with the highest level of multi-drug resistant TB.

Aim: To explore the sensitivity of a newly available molecular diagnostic method GeneXpert® (GX) in early detection of M tuberculosis (MT) and rifampicin (RIF) resistance.

Methods: Retrospective case control study. 360 respiratory samples (sputum and/or bronchial washings) from 320 subjects were tested with GX from 13/07/2010 (introduction of the method) till 01/11/2010. New pulmonary TB cases were analyzed.

Results: 100 patients had new pulmonary TB. GX was positive in 68 cases, matching in 3 cases also with MGIT® method (results available in 80 and 24 days respectively). In 6 cases out of 14 (40%) when RIF resistance detection concurred with LJ resistance, GX was positive in 9 cases (90%).

2 patients with negative LJ culture were GX positive. Resistance of MT against RIF on LJ media were detected in 14 cases and matched in 3 cases also with MGIT® method (results available in 80 and 24 days respectively).

Conclusions: GeneXpert® improves the diagnostic of pulmonary TB and allows faster detection of RIF resistance.

Table 1. Summary of the MT detection methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Tested (N of cases)</th>
<th>Positive (%)</th>
</tr>
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<td>96</td>
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<tr>
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<td>42</td>
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<tr>
<td>GX</td>
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<td>68</td>
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<tr>
<td>LJ</td>
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<tr>
<td>MGIT</td>
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</table>

P1822

A new integrated PCR and microarray lab-on-chip for rapid MDR tuberculosis diagnosis
Daniela M. Cirillo1, Andrea M. Cabibbe1, Paolo Miotto1, Elisa Lazzari1, Francesco Santoro3, Irina Kontseva1, Vladimir Nikolayevsky4, Gianni Pozzi2, Stefan Niemann1, Francis Dobrniowski5. 1Emerging Bacterial Pathogens Unit, Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy; 2Laboratory of Molecular Microbiology and Biotechnology (LAMMB), Department of Molecular Biology, University of Siena, Siena, Italy; 3Samara Oblast TB Service, Samara, Russian Federation; 4Queen Mary and Westfield College, University of London, London, United Kingdom; 5Molecular Mycobacteriology Group, National Reference Center for Mycobacteria, Forschungszentrum Borstel, Borstel, Germany

Introduction Drug-resistant M. tuberculosis (Mt) strains are a threat to tuberculosis (TB) control worldwide and more advanced, fast and affordable technologies are needed to strengthen laboratory capacity for diagnosis of multidrug resistant (MDR) cases.

Aims: The aim of the study is to develop a new rapid diagnostic tool for MDR-TB using a lab-on-chip (LoC) platform suitable for testing other poverty related diseases.

Methods: The LoC (In-Check™) provides an all-in-one device for fast amplification of target DNA followed by hybridization on a low-density microarray. Mt and most of the clinically relevant mycobacterial species are identified by specific probes targeting the 16S rRNA gene and IS6110. A multiplex PCR was developed to amplify rpOlb, katG, and inhA as the most frequently mutated genes involved in resistance to rifampin and isoniazid in species belonging the Mt complex.

Results: The In-Check™ platform was evaluated on isolates and smear positive clinical specimens. Selected probes allowed identification of Mt complex, and 10 clinically relevant non-tubercular mycobacterial species, including M. avium and M. intracellulare. The assay detects the following mutations involved in drug resistance: D516V, S531L (rpoB), S315T (katG), and c-153, t-8a, t-8c (inhA). Other mutations at codons 533, 526, (rpOlb), and 315 (katG) are identified by a negative signal from wild-type probes. Detection limit is 10³ bacteria/mL.

Conclusions: The In-Check™ platform represents an innovation for its simplicity of use, rapidity and cost-effectiveness and it is particularly suitable for different diagnostics purposes. This is the first device for molecular detection of malaria and TB on the same platform.

P1823

PCR for diagnosis of tuberculosis and pulmonary mycoses in México
Rubén Garrido1, Elisa Barrera2, Karla Cabada2. 1Department of Neurology and Thoracic Surgery, Specialty Medical Center, Ciudad Juárez, Chihuahua, Mexico; 2Institute of Biomedical Sciences, Autonomous University of Juarez, City, Ciudad Juárez, Chihuahua, Mexico

Introduction: Tuberculosis (TB) and pulmonary mycoses are a public health problem in the north of Mexico. We use polymerase chain reaction (PCR) for diagnosis of TB in patients with a negative bacilloscopy. This method also allows us to differentiate between other Mycobacterium and macroorganisms like the case of Histoplasma capsulatum, Coccidioides immitis and Aspergillus fumigatus.

Objective: The identification of Mycobacterium tuberculosis in patients showing clinical and radiological findings with negative bacilloscopies and its association with pulmonary mycoses.

Methods: Symptomatic patients with high pulmonary TB probability were selected by a complete physical exam, clinical history, thoracic x rays and bacilloscopy. In patients with a negative bacilloscopy an sputum sample was taken or a Bronchial-alveolar lavage to identify the presence of Mycobacterium, Histoplasma, Coccidioides and Aspergillus by PCR. Adequate treatment was administered according to the results obtained.

Results: A total of 23 patients were analyzed. The presence of Mycobacterium tuberculosis was found in 9 cases. In 5 subjects there was of Aspergillus fumigatus and in 4 cases of both. In 2 cases the presence of Mycobacterium tuberculosis, Histoplasma capsulatum, Coccidioides immitis were associated. Three samples were negative for all those microorganisms.

Conclusions: PCR’s sensibility and specificity increases the diagnosis of TB and mycoses cases. It is a magnificent tool when bacilloscopy is negative generating the need for use in the everyday medical practice. The use of innovative techniques for early diagnosis and treatment of frequent pulmonary disease in this region is imperative.

P1824

Relationship between rpOlb mutations and minimum inhibitory concentrations of rifampicin in multi drug resistant strains of mycobacterium tuberculosis
Shashikant Vaidya1, Vidyagouri Shinde2, Rupendra Jadhav3, Shreyasi Mulye4, Abhay Chowdhary5, Mohan Kulkarni1, Geeta Kopparkar4. 1Department of Microbiology, B.Y.L.Nair Charitable Hospital and T. N. Medical College, Mumbai, Maharashtra, India; 2Department of Immunology and Molecular Microbiology, Blue Peter Research Centre, Lepra Society India, Hyderabad, Andhra Pradesh, India; 3Department of Molecular Biology, Stanley Brown Laboratory, The Leprosy Mission, Delhi, India; 4Quality Control Department, Haffkine Bio-Pharmaceuticals Corporation Limited, Mumbai, Maharashtra, India; 5Director, Haffkine Institute for Training, Research and Testing, Mumbai, Maharashtra, India

Introduction: Rifampicin (RF) resistance serves as a surrogate marker for detection of multi drug resistant (MDR) strains of Mycobacterium tuberculosis (MTB). Among many mutations identified in rpOlb gene, the target gene for detection of RF resistance, few were verified by molecular genetic methods.

Federa...
Aim: To detect and characterize mutations in rpoB region of MDR MTB strains by automated DNA sequencing. To study the relationship between in vitro Minimum Inhibitory Concentrations (MIC) for RF and rpoB mutations.

Methods: Absolute concentration method was used to determine MIC of RF for 20 strains of MDR MTB strains. DNA sequencing was carried out in an ABI sequencer.

Results: We could detect point mutations in the 81 bp section of “a hot spot” region of the rpoB gene of all the MDR strains. Mutations were detected in positions 516,526 and 531, with frequencies of 30%, 40%, and 55%, respectively. It was found that mutations in positions 526 and 531 conferred high-level resistance to RF (MIC’s ≥ 128 μg/ml). Mutations in positions 516 relate to low-level resistance. (MIC’s ≤ 64 μg/ml).

Double point mutations in 2 isolates in positions 526 & 531 and 1 isolate in position 516 & 531 relate to high level resistance (MIC’s ≥ 128 μg/ml), while 2 isolates in position 516 & 526 relate to low level resistance (MIC’s ≤ 64 μg/ml).

Conclusion: A relationship between susceptibility to RF and alterations in rpoB gene is observed. However, relationship between gene alteration and drug-resistant phenotype is still unclear, further analysis of the relationship between MICs and gene alteration is necessary.

P1825
Hair-analysis for acetyl-isoniazid/isoniazid ratio and N-acetyl-transferase-2-genotype in patients on treatment for mycobacterium tuberculosis infection
Michael Eisenhut1, Detlef Thieme 2, Dagmar Schmid 3, Sybille Luederwald 3

Tuberculosis infection N-acetyl-transferase-2-genotype in patients on treatment for mycobacterium tuberculosis infection. Hair-analysis for acetyl-isoniazid/isoniazid ratio and P1825 gene alteration is necessary.

A relationship between susceptibility to RF and alterations in rpoB gene is observed. However, relationship between gene alteration and drug-resistant phenotype is still unclear, further analysis of the relationship between MICs and gene alteration is necessary.

Background: In the presence of non-compliance, drug malabsorption or widely spaced intermittent therapy genetically determined faster acetylation of isoniazid has been shown to lead to treatment failure and relapse. Hepatotoxicity and peripheral neuritis are associated with slow acetylation of isoniazid. Objectives were to investigate what determines hair-levels of isoniazid and to assess whether acetylator phenotype in form of the isoniazid/acetylisoniazid ratio in hair reflects N-acetylnicotinase – 2 (NAT-2) genotype.

Patients and methods: Hair was obtained from patients on isoniazid treatment. Isoniazid and acetyl isoniazid levels in hair were determined using HPLC/MS. Isoniazid and acetylisoniazid ratios were correlated with genotype of the NAT-2 determined by PCR. Hair levels of isoniazid were related to age, gender, weight, body mass index (BMI) and ethnic group.

Results: Hair levels of isoniazid and acetyl isoniazid were measured in 40 patients and genotype determined in 24. Hair levels of isoniazid correlated significantly with age and weight (p<0.05), but not with BMI or ethnic group. Acetylisoniazidisoniazid ratios were with a median of 15.2% (range 14.5 to 31.7, n=3) in homozygous rapid acetylator NAT-2 genotype and 37.3% (range 1.7 to 51.2, n=7) in the heterozygous rapid acetylator NAT-2 genotype both significantly higher than in the slow acetylator NAT-2 genotype with 5.8% (range 0.3 to 14.4, n=14).

Conclusion: Measured acetylation rates reflect NAT-2 genotype. Treg numbers in both healthy and asthmatic patients were analysed by multi-colour flow cytometry to quantify the CD4+CD25+FoxP3+ Tregs. Mild asthma patients had more CD4+CD25+FoxP3+ Tregs (6.1±2.6 in BAL and 3.9±1.6 in blood, but no difference between the prevalence in BAL lymphocytes from both groups was observed. RV16 provocation did not affect the CD4+CD25+FoxP3+ Treg numbers in blood and BAL in either patients with mild asthma or healthy controls. Conclusions: There is a higher number of CD4+CD25+ cells expressing FoxP3+ in peripheral blood of mild allergic asthma patients. Rhinovirus challenge did not have an impact on PBMC and BAL Treg numbers in both healthy and asthmatic individuals.

P1827
Pulmonary dendritic cells from chronic obstructive pulmonary disease patients suppress lung immune responses through induction of regulatory T cells
M. Tsoumakidou1,2, S. Tsoula3, E. Litsiou1, N. Panagiotou1, A. Panagiotou1, M. Konstantinou3, K. Patoris1, C. Roussos1, G. Xanthoulou1, S. Zakynthinos1

1 Lang Immunobiology, Thaurus, Athens, Greece; 2Cellular Immunology, Biomedical Research Foundation, Athens, Greece; 3Thoracic Surgery, Sotira Hospital, Athens, Greece

Defective Th immunity is considered to be implicated in the enhanced vulnerability of Chronic Obstructive Pulmonary Disease (COPD) patients to lower respiratory infections and lung cancer. Tolerogenic dendritic cells (DCs) and regulatory T cells (Tregs) are critical in the suppression of Th immunity. The role in COPD is elusive. We hypothesized that pulmonary DCs in COPD exhibit tolerogenic properties and suppress lung Th responses through induction of Tregs CD4+ DCs and CD3+ T cells were isolated from the lungs of COPD patients (n=17), smokers (n=16) and never-smokers (n=4). DC maturation prior and upon LPS exposure were examined. The effects of pulmonary DCs on lung Th cell responses and on the induction of Tregs were investigated. Pulmonary DCs from COPD patients and smokers express decreased levels of co-stimulatory molecules (CD40/80/86) compared to never-smokers at baseline (p<0.01). Upon LPS exposure, only DCs from COPD patients fail to upregulate costimulatory molecules. Pulmonary DCs from COPD patients induce decreased proliferation of autologous lung CD4+ and CD8+ T cells compared to DCs from smokers (p<0.001). CD4+ T cells treated with DCs from COPD patients, but not from smokers, express increased levels of the immunosuppressive cytokine IL-10 (p<0.01) and suppress Th responses in in vitro suppression assays. Our results reveal that lung DCs from COPD patients suppress lung immune responses through induction of Tregs. This novel immunoregulatory circuit has important clinical implications for the enhanced vulnerability of COPD patients to respiratory infections and lung cancer.

*These authors contributed equally. Funded by Thorax.
T-regulatory cells blood content in patients with asthma exacerbation
Zhannta Antanovich, Vladimir Tsarev, Natalya Goncharova. Propedeutics of Inner Diseases, Belarusian State Medical University, Minsk, Belarus
Background: Regulatory CD4+CD25+ T cells are important components of the immune system homeostasis and impairment of their activity can cause autoimmune diseases and allergy.
Objective: The aim of this study was to evaluate the blood content of naturally occurring T-regulatory cells (nTreg) in patients with different periods of asthma.
Methods: 48 steroid naive asthmatic adults with asthma exacerbation and 48 with asthma remission were randomly selected and 30 matched control subjects were included. All were submitted to detailed clinical history and examination, pulmonary function testing. Investigation of CD4+, CD4+CD25+, CD4+CD25hi lymphocytes in blood was carried out by flow cytometry. nTreg were defined as a fraction of CD4+CD25hi-lymphocytes with a high level of CD25 expression (CD4+CD25hi).
Results: Subjects with asthma exacerbation had significantly lower values of CD4+CD25hi-cells than subjects with asthma remission (1.56 (1.14-1.97)% vs 5.90 (4.96-6.71)%, p<0.001) and controls (1.56 (1.14-1.97)% vs 7.40 (6.41-8.52)%, p<0.001). Subjects with asthma remission had also significantly lower values of CD4+CD25hi-cells than controls (5.90 (4.96-6.71)% vs 7.40 (6.41-8.52%), p<0.001).
Conclusions: CD4+CD25hi-cells blood content is decreased in asthma in comparison with healthy subjects. Blood content of CD4+CD25hi-cells in asthma exacerbation decreases 3 fold and more in comparison with remission and can predict for asthma exacerbation.

Effector and regulatory lymphocytes in asthmatic pregnant women
Lilla Tamasi1, Anikő Bóhász1, Áron Cseh2, Noémi Eszes1, János Rigo Jr.3, Veronika Mülller1, Barna Vásárhelyi2, György Losonczi1. 1Department of Pulmonology, Semmelweis University, Budapest, Hungary; 2Department of Pediatrics, Semmelweis University, Budapest, Hungary; 31st Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary.
Asthma is one of the most common diseases that may complicate pregnancy. Asthma and pregnancy show bidirectional interactions with unknown immunological mechanisms. The aim of this study was to evaluate CD4+ regulatory T (Treg), natural killer (NK), NKT, invariant natural killer (iNKT), memory and naive CD4+ T lymphocytes in mild to moderate partially or well controlled persistant asthmatic pregnant patients.
The prevalence of lymphocyte subsets was identified by cell surface markers and intracellular FoxP3 staining, in healthy non-pregnant (HNP; N=15), healthy pregnant (HP; N=33), asthmatic non-pregnant (ANP; N=62) and asthmatic pregnant (AP; N=61) women. Data are given in median and quartiles.
Treg cell prevalence was higher in HP than in HNP subjects (7.82 (5.27-10.24)% vs 1.56 (1.14-1.97)%, p<0.05). The existence of IL-17+ cells in the granulomas also supports the role of Th1 cell responses against mKatG and PPD in sarcoidosis lung and peripheral blood cells. In the present study, IL-17 and IFN-γ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells. In the present study, IL-17 and IFNγ production were evaluated by ELISPOT after stimulation of bronchoalveolar lavage (BAL) fluid and peripheral blood cells.
The higher percentages of cytotoxic T cells in smokers and COPD patients compared to never-smokers (p<0.001). A higher frequency of CD27+CD45RA- cells and a lower frequency of CD27-CD45RA- cells was found in the CD4+ T cell population of COPD current smokers compared to never-smokers and COPD ex-smokers (p<0.005). Smokers with normal lung function had a higher percentage of CD4+CD27-CD45RA+ cells compared to never-smokers (p<0.05).

Conclusions: The higher percentages of cytotoxic T cells in smokers and COPD patients may be related to smoking-induced tissue damage. The increased percentage of central memory cells in COPD smokers suggests an ongoing immune response. Smoking cessation resulted in a normalization of CD4+ central/effector memory cells in BAL, indicating a reversibility of smoke-induced changes.

Background: Characterization of lymphocyte subsets in the lungs of smokers and patients with COPD.

Methods: Bronchoscopy and BAL was performed on 24 never-smokers, 20 smokers with normal lung function and 20 COPD patients (14 smokers and 6 ex-smokers). The frequencies of major lymphocyte subsets and the differentiation status of CD4+ and CD8+ T cells were analyzed by flow cytometry.

Results: There were higher percentages of CD90+ CD8+ T cells in smokers and CD56+ T cells in smokers and COPD patients compared to never-smokers (p<0.001). The observed downregulation of PPAR-alpha in T helper cells may contribute to ongoing inflammation in pulmonary sarcoidosis via failure to repress proinflammatory genes.

Methods: Seventeen sarcoidosis patients and nine healthy controls underwent bronchoscopy with broncoalveolar lavage (BAL) whereby CD4+ T cells and alveolar macrophages (AMs) were sorted by flow cytometry and subjected to real-time PCR analysis for mRNA expression of PPARs. Immunofluorescence staining of BAL cytospin slides with anti-PPAR antibodies was also performed.

Results: PPAR-alpha relative gene expression was significantly downregulated in COPD+ T cells of sarcoidosis patients, but no differences were observed with regard to T cell expression of the other PPARs. PPAR expression in AMs did not differ between patients and controls. No differences were observed between patients with COPD and healthy controls.

Conclusion: The observed downregulation of PPAR-alpha in T helper cells may contribute to ongoing inflammation in pulmonary sarcoidosis via failure to repress proinflammatory genes.

Background: Reduced expression of PPAR-alpha in bronchoalveolar lavage (BAL) differ in COPD patients compared to smokers with normal lung function and never-smokers.

Methods: Bronchoscopy and BAL was performed on 24 never-smokers, 20 smokers with normal lung function and 20 COPD patients (14 smokers and 6 ex-smokers). The frequencies of major lymphocyte subsets and the differentiation status of CD4+ and CD8+ T cells were analyzed by flow cytometry.
Ovalbumin (OVA)-sensitized C57BL/6 mice were exposed intranasally to OVA or PBS on five days and lung tissue was taken 24 h after final allergen exposure. Peribronchial (PB), perivascular (PV) and alveolar (A) tissue was selected from lung tissue sections using Laser Microdissection and Pressure Catapulting technology. Total RNA was extracted and each location was pooled from three OVA/OVA mice. Chemokine gene expression was performed using RT-PCR gene array. Tissue from which the tissue section of an OVA/PBS mouse was used as control and results were expressed as fold change from control. Chemokine ligands for Th1-associated receptors: CCRL1 (CCL2, CCL5, CCL7) and CCR1 (CCL3, CCL4) were increased mainly in a followed back and Pb tissue, while CCRL3 (CCL10) was increased in Pb followed by A and Pb tissue. In Th2-associated CCR8 (CCL8) was mostly highly induced Pb (21-fold) followed by A and Pb tissue. In Th2/Treg-associated CCR4 (CCL17, CCL22) the pattern was A, Pb, Pb, while in Treg/TTh1 CCRL7 (CCL19) was increased mainly in Pb then in Pb but not in A tissue.

Allergen exposure increased gene expression of all Th1, Th2, Treg and Th17 associated chemokines in lung. However, the expression pattern shows differences in both tissue distribution and magnitude, arguing for a high complex local milieu that can regulate T-cell subset distribution.

**P1840**

**T cell specific expression of a short splice variant of the tumor suppressor gene CYLD amplifies the development of allergic airway disease**

Sebastian Reuter, Marc Becker, Nina Dehazd, Helen Martin, Ari Waisman, Michael Stassen, Roland Buhl, Christian Taube. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany. Pulmonary Medicine, III Medical Clinic, Mainz, Germany.

Regulation of transcription factors like NF-kB decides about type and strength of developing inflammatory and immune responses. CYLD acts as a negative regulatory element of NF-kB activation, however the naturally occurring short splice variant CYLD<sup>Δ192</sup> (cCYLD) has positive regulatory properties. An exclusively expression of cCYLD leads to a hyperactive phenotype of dendritic cells (DC) and increased numbers of long living antibody secreting B cells. In the present study we determined the function of cCYLD on T cells in a murine model of allergic airway disease. Following sensitization and challenge towards the model antigen ovalbumin (OVA), wild type (WT) and animals with a T cell specific expression of CYLD<sup>Δ192</sup> (cCYLD) have positive regulatory properties. An exclusively expression of cCYLD leads to a hyperactive phenotype of dendritic cells (DC) and increased numbers of long living antibody secreting B cells.

In the present study we determined the function of cCYLD on T cells in a murine model of allergic airway disease. Following sensitization and challenge towards the model antigen ovalbumin (OVA), wild type (WT) and animals with a T cell specific expression of CYLD<sup>Δ192</sup> (cCYLD) have positive regulatory properties.
234. Phenotyping asthma: a clue for treatments?

1871
Late-breaking abstract: Genome-wide association of GLCCI1 with asthma steroid treatment response
Kei Ohtsu1, Yoko Sak sections, 2Thinichige Harada, Amy Murphy1, Augusto Litonjua1, Blanca Hines1, Christoph Lange1, Ross Lazarus1, Jody Sylvia1, Barbara Klanderger, Qinglian Duan2, Weiliang Qiu2, Tomomitsu Hirota2, Fernando Martinez1, Dave Mauger5, Christine Sorkness6, Stanley Szefler7, Stephen Lazarus4, Robert Lemanske3, Stephen Peters3, John Lima3, Yusuke Nakamura2, Mayumi Tamari2, Scott Weiss1.

Methods: We analyzed change in FEV1 following ICS usage in a small number of patients with asthma, whose mechanisms are currently insufficiently understood. We performed a genome-wide association study (GWAS) in 4,690 adults with asthma. A total of 93 patients and 100% of controls had severe asthma, according to Global Initiative for Asthma (GINA). The GWAS identified 12 independent SNPs significantly associated with ICS response, including 3 associated with GLCCI1. We then assessed the genetic effects of these SNPs by enriching the clinical phenotype.

Results: We identified a significant pharmacogenetic association at rs37973, which was replicated in four independent populations totaling 935 individuals (p<0.0007). This variant maps to the glucocorticoid induced transcript 1 (GLCCI1) gene and is in complete linkage disequilibrium (i.e., perfectly correlated) with rs37973, both are associated with decrements in GLCCI1 expression. In isolated cell systems the rs37973 variant is associated with significantly decreased dexamethasone receptor activity; in pooled data from treatment trials patients with the variant allele have reduced FEV1 response to ICS (pooled p=0.0007). Overall, subjects homozygous for the mutant rs37973 allele had only 0.5% increase on inhaled corticosteroids vs. those homozygous wild type (3.2±1.6% vs. 9.4±1.1%), accompanied by a significantly higher risk of a poor (i.e. lowest quartile) response (OR 2.36, 95% CI 1.54-3.51), with genotype accounting for ~6% of response variability.

Conclusion: A functional GLCCI1 variant is associated with substantial decrements in inhaled glucocorticoid response in asthma.

1872
Frequent exacerbators – A distinct phenotype of severe asthma
Maciej Kupczyk, Shoshila Haque, Roeleind Middelveld, Sven-Erik Dahlén, on behalf of the BIOAIR Study Group. EAAF, IMM, Karolinska Institutet, Stockholm, Sweden

In order to analyse exacerbations, 93 patients with severe asthma (SA) and 76 with mild-to-moderate asthma (MA) were screened and followed up for 1 year in the BIOAIR European multicentre study. Severe asthma has been defined by use of high doses of inhaled corticosteroids (>1000 μg/day of budesonide or equivalent) and despite this treatment at least 1 exacerbation in the year preceding the start of the study. Risk factors for frequent exacerbations (FE) (defined as either ≥2 or ≥3 events/year) were evaluated.

In total, 122 exacerbations were recorded, including 104 events in 52 SA patients (55.9% of SA cohort) and 18 events in 16 MA (22.2% of MA cohort). The average rate of exacerbations was 1.1 events per patient per year in SA and 0.2 events in MA. Significant decrease in PEF values, FEV1, increase in rescue medication use, day and night symptoms during exacerbations were recorded (p<0.05). All FE were found only in SA, not MA group. Jupepar ACQ score, sputum eosinophils≥2%, smoking history, quality of life, and FEV1≥70% were associated with the development of exacerbations in FE defined as ≥2 events/year (odds ratios OR: 5.0, 4.38, 3.8, 2.48, 2.34, respectively, p<0.05). BMI≥25, quality of life, smoking and Jupepar ACQ score were risk factors for exacerbations in FE defined as ≥3 events/year (odds ratios OR: 8.07, 6.7, 4.25, 4.14, respectively, p<0.05). Frequent exacerbators represent a distinct phenotype of severe asthma group. Identification of factors associated with a higher risk of exacerbations enables us to improve the standards of every day care in this subgroup of patients. Supported by EU (QLG1-CT-2000-01185), national funding bodies and the Other Initiative for Severe Asthma Research at KI.

1873
Is hypereosinophilic asthma a specific phenotype of asthma?
Pauline Pradère1, Yurlagui Uzunhan1, Jacques Cadier1, Anne Bergeron-Lafaurie3, Dominique Israël-Biet1, Gilles Garcia1, Stéphane Jouveshomme1, Muriel Varret1, Michel Aubert1, Bruno Crestani1, Camille Taille1, Hôpital Bichat-Claude Bernard, Paris, France; 2Service de Pneumologie, Hôpital Avicenne, Bobigny, France; 3Service de Pneumologie, Hôpital Tenon, Paris, France; 4Service de Pneumologie, Hôpital Antoine Béclère, Clamart, France; 5Service de Pneumologie, CHU Reims Dabos, Poissy, France; 6DIM, Hôpital Lapeyronie, Montpellier, France

Introduction: Blood eosinophilia > 1000/mm3 in patients with asthma should evoke particular forms of the disease, especially Chung-Strauss Syndrome (CSS) and allergic bronchopulmonary aspergillosis (ABPA). Little is known about patients who do not fulfill criteria for these diseases, usually referred as Hypereosinophilic Asthma (HA).

Aim of the study: To describe clinical and functional characteristics of patients with HA and to assess the prevalence of CSS and ABPA in asthma patients with blood hyper eosinophilia.

Methods: Retrospective study of 79 adult asthma patients with blood eosinophils count > 1000/mm3, compared with a control group of 30 asthma patients without blood hyper eosinophilia (<1000/mm3), defined as Non hyperEosinophilic Asthma (NEA).

Results: 90% of patients and 100% of controls had severe asthma, according to GINA. Main characteristics of the 4 groups are available on table 1.

<table>
<thead>
<tr>
<th>HA, n=47</th>
<th>CSS, n=18</th>
<th>ABPA, n=14</th>
<th>NEA, n=30</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>55±3</td>
<td>51±2</td>
<td>64±3</td>
<td>55±2</td>
</tr>
<tr>
<td>Sex (% of female)</td>
<td>37%</td>
<td>55%</td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>Total blood eosin (UEU)</td>
<td>52±1±43</td>
<td>770±199</td>
<td>1940±650</td>
<td>485±218</td>
</tr>
<tr>
<td>Blood eosinophils count (1/mm3)</td>
<td>2295±337</td>
<td>7180±1780</td>
<td>2570±272</td>
<td>258±147</td>
</tr>
<tr>
<td>Nasal polyposis (% patients)</td>
<td>50%</td>
<td>50%</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td>Atopy (% of patients)</td>
<td>42%</td>
<td>33%</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>Daily oral steroids use (% of patients)</td>
<td>28%</td>
<td>100%</td>
<td>50%</td>
<td>30%</td>
</tr>
</tbody>
</table>
| HA, Hyper eosinophilic Asthma; CSS, Chung-Stauss Syndrome; NEA, Non Eosinophilic Asthma.

Conclusion: When compared with the NEA group, HA seems to represent a subgroup of patients, mostly male, characterized by non atopic disease and high prevalence of nasal polyposis. CSS and HA share many similarities, suggesting an overlap between the diseases in some cases.

1874
Exhaled nitric oxide levels differ between allergic and non-allergic asthma in men, but not in women
Michiyoshi Imaoka. Internal Medicine, Fukuoka National Hospital, Fukuoka, Japan

Introduction: Several studies have shown potential gender specific differences in the pathophysiology and clinical presentation of asthma, whose mechanisms are not fully understood.

Frequent exacerbators represent a distinct phenotype of severe asthma group. Identification of factors associated with a higher risk of exacerbations enables us to improve the standards of every day care in this subgroup of patients. Supported by EU (QLG1-CT-2000-01185), national funding bodies and the Other Initiative for Severe Asthma Research at KI.

321s Farmaceutici SpA. Visit Chiesi Farmaceutici SpA, at Stand D.30
Aims and objectives: We examined the effect of gender on differences in eosinophilic airway inflammation between steroid-naive adults with allergic and non-allergic asthma.

Methods: The subjects comprised 191 Japanese adults (67 men and 124 women, median [range] age 51 (20-88) years) who were untreated with glucocorticosteroids and during attack-free periods. We used the levels of fractional expired nitric oxide (FeNO) as a marker of eosinophilic airway inflammation. The FeNO concentration was measured using the recommended online method.

We compared the levels of FeNO between patients with allergic and non-allergic asthma separately for men and women.

Results: In 67 men, 49 patients had significantly higher FeNO levels compared with 18 non-allergic patients (53.9±4.6 versus 28.3±18.8 ppb, respectively; \( P<0.005 \); in 124 women, there was no significant difference in FeNO levels between 76 allergic and 48 non-allergic patients (38.0±37.0 versus 33.5±26.3 ppb respectively; \( P=0.4 \)).

Conclusions: Our results suggest that the importance of eosinophils in airway inflammation differs between allergic and non-allergic asthmatics, men and women. Other inflammatory cells than eosinophils alone may play a major role in the pathogenesis in men with non-allergic asthma.

1875

Does systematic assessment improve healthcare outcomes and healthcare utilisation in patients with severe asthma?

Suzanne Regan, Farhana Shor; Markus Hofmann, Andrew Menzies-Gow

1 Respiratory Medicine Division, Royal Brompton Hospital NHS Trust, London, United Kingdom; 2 Respiratory Medicine Division, Imperial College Healthcare NHS Trust, London, United Kingdom

Introduction: The management of severe asthma remains a significant problem in terms of patient symptoms, quality of life, effects of high dose oral corticosteroid therapy and emergency healthcare utilisation. The key to the effective management of severe asthma lies with making the correct clinical diagnosis. A systematic approach to aid effective diagnosis, identify co-morbidities and evaluate adherence was first introduced in 1993 and is now widely used. Little published data currently exists on the longer term benefits of utilising a systematic approach.

Methods: A retrospective audit of 68 patients that underwent a systematic assessment protocol at the Royal Brompton Hospital between April 2009 and March 2010 was performed. The magnitude of improvement in asthma related quality of life, exacerbation frequency, emergency healthcare utilisation and oral corticosteroid requirements was assessed.

Results: The table below represents a selection of demographic data, confirmation of diagnosis, mortality rate, discharge and lost to follow up rates. Further data is being analysed and will be presented at the congress including the outcomes for quality of life, healthcare utilisation and changes to treatment regimes.

Baseline data from systematic assessment of asthma

<table>
<thead>
<tr>
<th>Gender</th>
<th>Confirmation</th>
<th>Discharged</th>
<th>Died</th>
<th>Co-morbidity follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 25 (37%)</td>
<td>Female 43 (63%)</td>
<td>59 (87%)</td>
<td>34 (58%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

Conclusions: Systematic assessment of patients with difficult asthma identifies an alternative diagnosis in 13% of patients and one or more co-morbidity in 58% of patients referred to the difficult asthma service at the Royal Brompton Hospital.

1876

Improvement of asthma control by a concomitant therapy with cineole

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With its proven mucolytic and anti-inflammatory effects it is hypothesized that cineole as a main constituent of eucalyptus oil, improves asthma control. In a double blind, placebo controlled multi-centre-study 247 patients with symptomatic asthma were randomly administered 3x200 mg of cineole (n=126;mean age, 52.3 years) or a placebo (n=121;mean age,53.5 years), per day as a concomitant therapy over 6 months.

The combined primary outcome measures, which were implemented as a multiple criteria testing process were: improvement of FEV1, asthma symptoms and quality of life (AQLQ). Secondary outcome measures included changes in hypersecretion, various respiratory symptoms, and the use of ICS.

Results: 1 Patients treated with cineol showed significantly more improvements to the multiple testing criteria (i.e. improvement of FEV1,p=0.0398; mean improvement of AQLQ, p=0.0475; symptom score of nocturnal asthma, p=0.0325) as compared to placebo group, (p=0.0027, Wei Lachin test).

2. Secondary outcome measures supported these findings showing reduced dyspnea and cough as well as overall better health condition amongst the cineole treatment group.

3. Adverse events were comparable in both groups.

Conclusion: Concomitant therapy using cineol can lead to improvement in asthma symptoms, lung function and quality of life. This study underlines the fact that cineole actively controls airway inflammation in patients with asthma, and that it is more that simply a mucolytic drug.

1877

Pragmatic controlled trial of azithromycin for asthma in adults

David Hahn, Michael Graumack; Scott Hetzel

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Background: Macrolides are a novel treatment for asthma.

Methodology: To investigate macrolide effects after treatment.

Methods: Randomized (RAND), placebo-controlled, double-blind parallel group, practice-based trial of azithromycin (AZ), 600 mgm for 3 days, then weekly for 11 weeks or placebo (PLA) with follow up 1 year from randomization. Eligible subjects who declined randomization received open-label (OL) azithromycin.

Results: Compared to RAND, OL subjects had more adult-onset asthma, chronic sinusitis, severe persistent asthma and hospitalizations for asthma. Compared to PLA, OL subjects had significant improvements in asthma symptoms and quality of life (QOL) at 1 year (9 months post-treatment). AZ subjects did not have comparable benefits (Table).

Outcomes at 1 year compared to pretreatment

<table>
<thead>
<tr>
<th>Mean paired difference (SD)</th>
<th>PLA, n=20</th>
<th>AZ, n=29</th>
<th>OL, n=13</th>
<th>P-value, OL v PLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall asthma symptoms</td>
<td>-0.10 (1.07)</td>
<td>-0.07 (0.88)</td>
<td>-1.07 (0.95)</td>
<td>0.011</td>
</tr>
<tr>
<td>Control</td>
<td>-0.45 (1.00)</td>
<td>-0.34 (0.88)</td>
<td>-1.08 (1.20)</td>
<td>0.132</td>
</tr>
<tr>
<td>QOL</td>
<td>0.40 (1.31)</td>
<td>0.50 (1.01)</td>
<td>1.70 (1.42)</td>
<td>0.155</td>
</tr>
</tbody>
</table>

The proportions of subjects achieving a QOL score change ≥1 unit at 9 months (6 months after finishing treatment) were 22% for PLA, 27% for AZ and 80% for OL (p<0.001 compared to PLA). At 1 year the comparable figures were 21%, 36% and 54% (P=0.072).

Conclusions: OL subjects had severe asthma and persistent benefits, number needed to treat (NNT) = 2 to 4. AZ subjects had milder asthma and did not show benefits. Though this study was not powered to detect the NNT = 7 suggested by some results. Azithromycin should be considered as adjunctive therapy for severe asthma unresponsive to guideline treatments. Larger studies are warranted to confirm results in severe asthma and to explore potential benefits in milder asthma.

1878

Persistent asthma and long-term work disability

Paula Kauppi, Rina Hakola, Timo Lemo, Anna Ojijärvi, Jaana Pentti

1 Tiula Oksanen, 2 Tari Haahrta, 3 Mika Kissian, 4 Jussi Valthera. 1Allergyology, Skin and Allergy Hospital, Helsinki, Finland; 2Organisation and Management, Finnish Institute of Occupational Health, Helsinki, Finland; 3Organisation and Management, Finnish Institute of Occupational Health, Turku, Finland

Background: Mortality in asthma is very low but the disease has effects on quality of life and work ability. Here, the probability of long-term work disability associated with asthma alone or asthma together with chronic comorbidity(ies) was studied.

Methods: A total of 2 332 asthmatic employees in public sector in Finland were used for long-term (≥90 days) work disability. Employees without asthma were used as control subjects (N=66 354) and were adjusted for age, gender, socioeconomic status, type of employment contract and type of organization. Diagnosis of asthma was based on reimbursement for asthma medication granted by the Social Insurance Institution and data on all sickness absences were obtained from national registers. Six main disease categories were used in this study as comorbidity for asthma: depression, ischemic heart disease, diabetes, rheumatic disease, malignancy and hypertention. Diagnoses for comorbidities were based on the reimbursement for disease medication by the Social Insurance Institution.

Results: Asthma increased the risk of all-cause work disability with HR 1.8 (95% CI 1.6-2.1) compared to controls (no asthma). Asthma and one other chronic co-morbidity increased the risk for work disability with HR 2.2 (95% CI 1.8-2.8). Asthma together with two or more other chronic conditions increased the risk with HR 4.5 (95% CI 3.0-6.8). Depression together with asthma increased the risk of long-term work disability threefold compared to those without asthma.

Conclusions: Asthma alone or together with another chronic comorbidity increased the risk of long-term work disability and the risk was especially high for those with asthma and depression.
Assessment of relative regional lung compliance in patients with COPD

Alexandra Morgan1,2, Geoff Parker1,2, Penny Hubbard1,2, David Singh1,3, Jørgen Vestbo1,2, Simon Young1, Eva Bondesson4, Lars Olsson6, Lars Wigsström4, Josephine Naish1,2.

1Imaging Sciences, School of Cancer and Enabling Sciences, University of Manchester, Manchester, United Kingdom; 2The Biomedical Imaging Institute, University of Manchester, Manchester, United Kingdom; 3AstraZeneca, R&D, Alderley Park, Macclesfield, United Kingdom; 4AstraZeneca, R&D, Mölndal, Sweden; 5AstraZeneca, R&D, Alderley Park, Macclesfield, United Kingdom; 6AstraZeneca, R&D, Charnwood, United Kingdom.

Pathologically altered lung mechanical properties are difficult to assess regionally. A method has been developed utilising structural proton MRI in conjunction with post-processing and image registration techniques to provide measures of relative regional lung compliance [1].

This method was applied in 23 COPD patients and 11 healthy controls. Each subject had two supine scans, 1 week apart. Compliance maps were found to be reproducible, with increased spatial heterogeneity seen in patients compared to controls (Figure 1).

Figure 1. Relative regional compliance maps for healthy controls and COPD patients (mapped on log scale).

The gradient of relative compliance from lung apex to diaphragm was calculated. An increased compliance gradient was seen in moderate COPD (p<0.05), with a more significant increase in severe COPD (p<0.001) (Figure 2).

Figure 2. Box plot of relative compliance gradients (found using relative regional compliance and position as fraction of lung length).

The method shows significant differences between COPD patients and healthy controls with areas of altered relative regional compliance indicating likely regions of disease.

Reference:

Novel ventilation-perfusion ratio measurements in COPD using MRI

Penny L. Hubbard1,2, Geof J.M. Parker1,2, Dave Singh1, Jørgen Vestbo2,3, Eva Bondesson3, Lars E. Olsson5, Lars Wigsström4, Simon S. Young5, Josephine H. Naish1,2.

1Imaging Sciences, School of Cancer and Enabling Sciences, The University of Manchester; 2Manchester Academic Health Sciences Centre, Manchester, United Kingdom; 3The Biomedical Imaging Institute, University of Manchester, Manchester, United Kingdom; 4Airway Pharmacology Group, School of Translational Medicine, University Hospital of South Manchester, Manchester, United Kingdom; 5AstraZeneca, R&D, Charnwood, United Kingdom; 6AstraZeneca, R&D, Lund, Sweden; 7AstraZeneca, R&D, Mölndal, Sweden; 8AstraZeneca, R&D, Alderley Park, Macclesfield, United Kingdom.

We present a novel analysis of oxygen-enhanced (OEMRI) data in COPD that allows quantitative ventilation-perfusion ratio (V/Q) maps to be determined. Representative V/Q maps of: A healthy, B moderate & C severe COPD subjects reveal homogeneous maps for A and considerable heterogeneity in B/C.

Group-average histograms (labelled as above) show a narrow peak in A; the peak broadens and a lower V/Q peak becomes evident in B/C. A high V/Q tail is also seen in C.

OEMRI parameters, enhancing fraction (EF) and interquartile range (IQR) V/Q, show significant differences between A & B/C. Each group had 12 subjects, data averaged over 2 scans. Using a single slice, minimum group sizes to detect a 50% difference of the healthy group window are 27 (EF) & 14 (IQR V/Q).

Power calculations are specific to this implementation of the methods, we envisage improvements with further development.

Group mean and SD for OEMRI parameters

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>0.87±0.06</td>
<td>0.70±0.09*</td>
<td>0.68±0.11*</td>
</tr>
<tr>
<td>IQR-V/Q</td>
<td>0.55±0.13</td>
<td>0.80±0.16*</td>
<td>0.81±0.12*</td>
</tr>
</tbody>
</table>

*Significantly different to healthy (p<0.05).

The results show strong similarities to published literature using more invasive techniques and enable powering of future intervention studies.

Repeatability of MR imaging in chronic obstructive pulmonary disease (COPD)

Sebastian Ley1, Angela Anjorin2, Julia Ley-Zaportniz1, Annette Opgenorth2, Oliver Sedlacek2, Claus-Peter Heussel1, Hans-Ulrich Kaucer2.

1Department of Medical Imaging, University of Toronto, Toronto, ON, Canada; 2Department of Diagnostic and Interventional Radiology, University Hospital of Heidelberg, Heidelberg, Germany; 3Department of Diagnostic and Interventional Radiology, Thoraxklinik at the University of Heidelberg, Heidelberg, Germany.

Purpose: COPD is a broad disease entity defined by PFT, however providing only a global measure of the disease. With the increasing number of therapeutic options, particularly when it is advanced, there is a high demand for a non-invasive imaging test to identify different phenotypes providing regional information on structural and functional changes in order to target therapies accordingly. Recent developments have opened the way for introduction of proton MRI of the lung into the clinical arena. This technique allows for radiation free assessment of the above mentioned issues. So far, no data regarding the repeatability of this technique is available.

Materials/Methods: A comprehensive MR protocol (1.5T) was developed to investigate different aspects of the disease. The protocol consisted of morphological, pulmonary perfusion, cardiac function and respiratory dynamics sequences. Overall, 9 patients (COPD stages IIb/IV) were investigated twice in a 24h interval.

Results: The mean examination time was 64min and all patients tolerated the examination well. Visual evaluation of morphological and perfusion sequences demonstrated a good repeatability of the visualization of the parenchymal loss and perfusion deficits. Quantitative evaluation of flow measurements revealed considerable variations (interexamination difference for the PA flow: 7-64ml). Evaluation of the respiratory dynamics showed a broad variation allowing for no meaningful interpretation.

Conclusions: Overall, the proposed imaging protocol is feasible and applicable even in significantly ill COPD patients. The protocol is easy to use and shows a high repeatability in the key aspects for assessment of morphological and functional disease components.
1882 Ventilation-perfusion mismatch in COPD with or without emphysema: Comparison of structural CT and functional OE-MRI
Weijian Zhang1,2, Penny Hubbard1,2, Eva Bondesson1, Lars Wigstrom1, Simon Young3, Dave Singh4, Geoffrey Parker1,2, Josephine Nash1,2. Imaging Sciences, School of Cancer and Enabling Sciences, University of Manchester; Manchester Great Manchester, United Kingdom; The Biomedical Imaging Institute, University of Manchester, Manchester Great Manchester, United Kingdom; R&D, Astrazeneca, Lund, Sweden; R&D, Astrazeneca, Charnwood, United Kingdom; Medicines Evaluation Unit, University Hospital of South Manchester, Manchester, United Kingdom

Single-slice conoral oxygen-enhanced MRI (OE-MRI) images were acquired in 24 patients with chronic obstructive pulmonary disease (COPD) and 12 healthy subjects, from which color-coded V/Q maps were extracted by pixelwise model fitting. COPD were structurally classified by percentage of low attenuation areas under -950 HU (LAA%) in matched single-slice CT images: LAA%<1%—non-emphysematous COPD; ≤1%—emphysematous COPD, which demonstrates that comparative V/Q mismatch exists in COPD even if there is no emphysema. To explore potentially different structure-function relationship in two COPD types, correlation between CT and OE-MRI parameters was measured. Median V/Q did not correlate with LAA% in COPD. However, inter-quartile range of V/Q, representing the extent of heterogeneity, was fairly correlated with LLA% in emphysematous COPD. However, inter-quartile range of V/Q, representing the extent of heterogeneity, was fairly correlated with LLA% in emphysematous COPD. Nevertheless, V/Q mismatch in COPD gets worse as emphysema increases. However, the correlation was not found in non-emphysematous COPD.

1883 Decline in lung density is accelerated in active smokers
Sahar B. Shaker1, Asger Dirksen1, Pechun Lo2, Lene T. Skovgaard3, Lars Wigstrom1, Marleen de Bruijn3, Jesper H. Pedersen4. 1Dept. of Respiratory Medicine, Gentofte Hospital, Copenhagen, Denmark; 2Dept. of Biostatistics, University of Copenhagen, Copenhagen, Denmark; 3Dept. of Biostatistics, University of Copenhagen, Copenhagen, Denmark; 4Dept. of Thoracic Surgery, Rigshospitalet, Copenhagen, Denmark

This study elucidates that distinction between emphysematous COPD and non-emphysematous COPD does not affect the presence of V/Q imbalance substantially but that the relationship between V/Q and CT measures vary between these two types.

1884 The relationship between airflow limitation and quantitative computed tomographic assessment of air trapping and emphysema
Omo M. Muts1, Keelin Murphy2, Pieter Zanen1, Hester A. Gietsma1, Jan Willem Lammers1, Bram van Ginneken3, Mathias Prokop1,2, Pim A. de Jong1. 1Radiology, University Medical Center Utrecht, Utrecht, Netherlands; 2Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands; 3Pathology, University Medical Center Utrecht, Utrecht, Netherlands; Diagnostic Image Analysis Group, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; Radiology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Background: Small airways disease and emphysema are the main components of airflow limitation in COPD. The independent contribution of quantitative CT measurements of these components to airflow limitation in COPD is yet unknown.

Purpose: To determine to what extent the combination of quantitative CT measurements of air trapping and emphysema can explain the variance in lung function in a population that covers the total spectrum of airflow limitation.

Methods: We studied 248 subjects (50 without airflow limitation; 50 GOLD 1; 50 GOLD 2; 50 GOLD 3; 48 GOLD 4) with paired inspiratory and expiratory CT (corrected for sex, age and height) the combination of CT emphysema and CT air trapping explained 68% to 83% (p<0.001) for percentage of voxels <−850 Hounsfield units (EXP−850) and FEV1/FVC. In multivariate analysis (corrected for sex, age and height) the combination of CT emphysema and CT air trapping explained 68% to 83% (p<0.001) of the variance in lung function parameters of airflow limitation (FEV1, FEV1/FVC, RV/TLC and Kco).

Results: Quantitative CT measurements were strongly related to airflow limitation, the best univariate R-square value was 0.72 (p<0.001) for percentage of voxels <−850 Hounsfield units (EXP−850) and FEV1/FVC. In multivariate analysis the combination of CT emphysema and CT air trapping explained 68% to 83% (p<0.001) of the variance in lung function parameters of airflow limitation (FEV1, FEV1/FVC).

Conclusion: Quantitative CT air trapping and emphysema measurements are strongly associated with lung function impairment, and when combined they explain a large part of the variance in airflow limitation. Our results may prove useful in automated detection and phenotyping of COPD cases.

1885 Computer modelling and visualisation of the microscopic distributions of hyperpolarized gas diffusivity in models of acinar airways
Juan Parra-Robles, Xiaojun Xu, Jim M. Wild. Unit of Academic Radiology, University of Sheffield, Sheffield, United Kingdom

Diffusion MRI using hyperpolarized gases is sensitive to lung microstructure. Computer simulations used to investigate the relationship between diffusivity (ADC) and airway dimensions are generally limited by non-realistic geometric assumptions (e.g. infinite cylindrical airways). In this work, we use histology sections to generate realistic models of acinar airways that are used in a computer simulation of 3He and 129Xe gas diffusion and 129Xe exchange between gas and tissue.

Results: The different diffusivities of 3He (A) and 129Xe (B) result in different ADC (in cm2/s) distributions.

For 3He, the distribution over the largest airway is nearly uniform due to motional averaging; the best univariate R-square value was 0.72 (p<0.001) for percentage of voxels <−850 Hounsfield units (EXP−850) and FEV1/FVC. In multivariate analysis (corrected for sex, age and height) the combination of CT emphysema and CT air trapping explained 68% to 83% (p<0.001) of the variance in lung function parameters of airflow limitation (FEV1, FEV1/FVC).

Conclusion: Quantitative CT air trapping and emphysema measurements are strongly associated with lung function impairment, and when combined they explain a large part of the variance in airflow limitation. Our results may prove useful in automated detection and phenotyping of COPD cases.
Conclusion: Computer simulation and visualization of maps of microscopic diffusion distributions in realistic acinar geometries have helped provide a better understanding of the length scales and diffusion regimes relevant to hyperpolarized gas lung MRI and may help simplify the development of 129Xe-based MR lung morphometry techniques.

236. The best abstracts in rehabilitation and chronic care 2011 (sponsored by Nutricia Advanced Medical Nutrition)

1886 Late-breaking abstract: Wii Fit™-step is a suitable exercise in rehabilitation programs in patients with COPD: A feasibility study Tanguy Marquette1, Fabien Lassus2, Olivier Castagna2, Daniel D’Amore2, Bruno Escarguel2, Louis Marquette2, 1UMR CNRS 6233 - Institut des Sciences du Mouvement, Université de la Méditerranée, Marseille, France; 2Service de Pneumologie, Centre Hospitalier Intercommunal de Toulon - La Seyne, Toulon, France

Patient with COPD can be involved in pulmonary rehabilitation programs, by using cycle ergometer exercises. They often give up with this exercise either during the program or when they have to manage it themselves. We conducted a randomised double-blind, placebo controlled trial. 59 patients (mean [SD] age 67.9±1.9y, BMI 26.7±4.7) were visited within each session.

Within Group Change Between Group Mean Difference

<table>
<thead>
<tr>
<th>Within Group Change</th>
<th>PS (n=30)</th>
<th>Placbo (n=29)</th>
<th>Between Group Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isometric strength</td>
<td>19.8 (12.2 to 27.9)**</td>
<td>16.6 (9.5 to 23.6)**</td>
<td>3.2 (–7.0 to 13.1)</td>
</tr>
<tr>
<td>Isokinetic strength</td>
<td>17.7 (10.2 to 25.2)**</td>
<td>19.8 (13.0 to 26.6)**</td>
<td>–2.1 (–12.0 to 7.9)</td>
</tr>
<tr>
<td>Thigh lean mass</td>
<td>180.1 (102.2 to 258.0)**</td>
<td>230.4 (140.0 to 320.7)**</td>
<td>–50.3 (–166.7 to 66.2)</td>
</tr>
<tr>
<td>Peak cycle work</td>
<td>9.9 (4.2 to 15.7)*</td>
<td>8.2 (3.5 to 12.8)*</td>
<td>1.7 (–5.4 to 8.9)</td>
</tr>
<tr>
<td>Peak cycle VO2</td>
<td>0.5 (–1.9 to 2.8)</td>
<td>2.3 (0.1 to 4.5)*</td>
<td>–1.9 (–5.0 to 1.3)</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.001 within group change.

Conclusion: There were significant improvements in quadriceps strength, thigh mass & whole-body cycle work following RT. The addition of PS did not augment the functional benefits of RT.

1887 Obstructive lung disease is associated with increased abdominal visceral fat and elevated systemic adipocytokines Bram van den Borst1, Harry Gooker1, Annemarie Koster2, Daisy Janssen1,2,3, Martijn Spruit1, Jos Schols4, Bianca Cox5, Tim Nawrot5, Randall Curtis6, Emiel Wouters1,7. 1Program Development Centre, Cour, Horn, Netherlands; 2CAPHR, Maastricht University, Maastricht, Netherlands; 3Centre for Interdisciplinary Treatment, Proteon Thuis, Horn, Netherlands; 4Department of General Practice, Nursing Home Medicine, Faculty of Health and Life Sciences/CAPHR, Maastricht University, Maastricht, Netherlands; 5Division of Pulmonary, Allergy & Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, United States; 6Medicine, Epidemiology & Biostatistics, University of California, San Francisco, CA, United States

Background: The source of systemic inflammation in clinically stable Obstructive Lung Disease (OLD) is unknown. Visceral adipose tissue (VAT) is related to systemic inflammation. We hypothesized that in OLD subjects a redistribution of VAT area (VAT) was performed successfully matching n=729 non-OLD controls to the cases.

| Status and pack years for the n=2139 subjects, and 3:1 propensity score matching was performed successfully matching n=729 non-OLD controls to the cases. |
|----------------------|----------------------|----------------------|----------------------|----------------------|
| Controls: compared to cases, had greater VAT area (143±47 vs 123±59 cm², p<0.001) and elevated interleukin (IL)-6 (2.16 [1.52-3.34] vs 1.75 [1.20-2.69] pg/ml, p<0.001). Plasma adiponectin Inhibitor-1 (PAI-1) (2.2 [12-37] vs 18 [11-31] ng/ml, p=0.008) and adiponectin (11 [7-16] vs 10 [6-15] μg/ml, p=0.037). Neither whole-body nor appendicular/trunk fat mass were different between cases and controls (p<0.05).

Conclusion: This study shows that OLD patients have greater VAT and elevate systemic IL-6, PAI-1 and adiponectin levels compared to non-OLD controls matched for sex, age, race, BMI and smoking. Greater VAT in OLD may reflect a disturbed metabolic regulation contributing to systemic pathology. Performed within Ti Pharma project T1-2011.

1888 Does protein supplementation enhance the effects of resistance training in patients with COPD? Linxy Houchen1,2, Manoj Menon1, Samantha Harrison1, Carolyn Sandiland2, Michael Morgan3, Sally Singh1,2, Michael Steiner1, 1Institute for Lung Health, Glenfield Hospital, Leicester, United Kingdom; 2Faculty of Health & Life Sciences, Coventry University, Coventry, United Kingdom; 3Respiratory Medicine, University of Leicester, Leicester, United Kingdom

Introduction: Protein supplementation (PS) & resistance training (RT) enhances muscle growth in healthy elderly subjects. Its role in patients with COPD is unknown.

Hypothesis: Adding PS to RT will yield greater increases in function than RT alone.

Method: We conducted a randomised, double-blind, placebo controlled trial. 59 patients (mean [SD] age 67.9±1.9y, BMI 26.7±4.7, FEV1% of the maximal HR on cycle ergometer and at 56.4±9.9% of the maximal HR on cycle ergometer and at 56.4±9.9%) underwent two sessions of incremental exercise to their limit of tolerance first on a cycle ergometer, and then on Wii Fit step game by adjusting the frequency of movements and the step height.

Methods: 265 clinically stable outpatients with COPD, CHF or CRF were visited during follow-up. The odds ratio (95% CI) combining the time and factor effects show CPR and MV preferences changed in 38% of the patients during follow-up.

| Status and pack years for the n=2139 subjects, and 3:1 propensity score matching was performed successfully matching n=729 non-OLD controls to the cases. |
|----------------------|----------------------|----------------------|----------------------|----------------------|
| Controls: compared to cases, had greater VAT area (143±47 vs 123±59 cm², p<0.001) and elevated interleukin (IL)-6 (2.16 [1.52-3.34] vs 1.75 [1.20-2.69] pg/ml, p<0.001). Plasma adiponectin Inhibitor-1 (PAI-1) (2.2 [12-37] vs 18 [11-31] ng/ml, p=0.008) and adiponectin (11 [7-16] vs 10 [6-15] μg/ml, p=0.037). Neither whole-body nor appendicular/trunk fat mass were different between cases and controls (p<0.05).

Conclusion: This study shows that OLD patients have greater VAT and elevate systemic IL-6, PAI-1 and adiponectin levels compared to non-OLD controls matched for sex, age, race, BMI and smoking. Greater VAT in OLD may reflect a disturbed metabolic regulation contributing to systemic pathology. Performed within Ti Pharma project T1-2011.

1889 Stability of life-sustaining treatment preferences of patients with advanced chronic organ failure Daisy Janssen1,2, Martijn Spruit1, Jos Schols3, Bianca Cox4, Tim Nawrot5, Randall Curtis6, Emiel Wouters1,7. 1Program Development Centre, Cour, Horn, Netherlands; 2CAPHR, Maastricht University, Maastricht, Netherlands; 3Centre for Interdisciplinary Treatment, Proteon Thuis, Horn, Netherlands; 4Department of General Practice, Nursing Home Medicine, Faculty of Health and Life Sciences/CAPHR, Maastricht University, Maastricht, Netherlands; 5Division of Environmental Sciences, Hasselt University, Diepenbeek, Belgium; 6Division of Pulmonary & Critical Care Medicine, Department of Medicine, Harbormov Medical Center, Seattle, United States; 7Respiratory Medicine, Maastricht University Medical Center + (MUMC+), Maastricht, Netherlands

Objectives: We aimed to investigate 1-year stability of preferences regarding cardiopulmonary resuscitation (CPR) and mechanical ventilation (MV) of patients with advanced COPD, chronic heart failure (CHF) or chronic renal failure (CRF), and to identify clinical determinants associated with these preferences.

Methods: 265 clinically stable outpatients with COPD, CHF or CRF were visited at baseline and every 4 months for 1 year, to assess preferences for CPR and MV. Generalized estimating equations were used to study the association between preferences and several potential predictors including co-morbidities, hospital admissions, health status (EQ5D), care dependency (CDS), mobility, depression (HADS-D) and anxiety (HADS-A).

Results: 78% of the patients completed 1 y follow-up (64% men; mean [SD] age: 67 (13) yrs). CPR and MV preferences changed in 38% of the patients during follow-up. The odds ratio (95% CI) combining the time and factor effects show...
an association between preference for CPR and change in EQ5D (+1 pt; OR 1.7 (1.2-2.5)), CDS (+9 pt; OR 1.5 (2.1-2.9)), HADS-D (+5 pt; OR 0.5 (0.3-0.9)) and change in marital status (single vs. living with partner: OR 0.5 (0.3-0.9)), and an association between preference for MV and change in EQ5D (+1 pt; OR 1.5 (1.1-2.2)), CDS (+9 pt; OR 1.5 (1.1-1.9)) and HADS-D (+6 pt; OR 0.6 (0.4-0.8)).

Conclusions: More than a third of outpatients with advanced COPD, CHF or CRF changed their preferences regarding CPR and/or MV during 1 year at least once. Regular re-evaluation of advance care planning is necessary when patients experience a change in health status, care dependency, mood status or marital status.

1890 Effect of resistance training during hospitalization in the systemic inflammation, functional capacity and muscle strength in COPD patients

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Background: Resistance training (RT) during hospitalization improves skeletal muscle strength; however its effect on systemic inflammation and to modify the level of activity remains unknown.

Objective: Our aim was to evaluate the effect of RT in the systemic inflammation and functional capacity in COPD patients during and after hospitalization.

Methods: Twenty nine out 102 patients hospitalized due to COPD exacerbation were randomly assigned to either Control (CG) or RT (RTG) groups. They were evaluated on the 2nd day of hospitalization, at hospital discharge and after 30 days. It was evaluated systemic inflammatory markers (TNF-α, RCP, IL-1β, IL-12p70, IL-6, IL-8) level of physical activity, health-related quality of life (HRQL), and upper and lower limbs muscle strength.

Results: Patients from RTG showed an improvement in the lower limb muscle strength, in the six-minute walking test (6MWT) and in all domains of HRQL (p<0.001). In contrast, CG showed a reduction in the lower limb muscle and 6MWT and a worsening in the HRQL. None of the differences between groups was observed in the systemic inflammatory markers analyzed during hospitalization and after 30 days of hospital discharge. In addition, most patients from both groups remained physically inactive (70%) in the hospital and at home.

Conclusion: Our results suggest that resistance training during hospitalization improves lower limbs muscle strength, health-related quality of life and physical capacity; however does not change either systemic inflammatory levels or physical activity during or after hospital discharge.

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1891 Effects and feasibility of different types of endurance training in patients with end stage lung disease before lung transplantation

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Objective: Aim of this study was to compare the effects and the feasibility of continuous moderate endurance training (CT) versus high-intensity interval training (IT) in patients with end-stage COPD before lung transplantation (pre-LTx) during a specialized 3-week in-patient pulmonary rehabilitation programme.

Methods: 60 lung transplant candidates (age: 53.5±5.6 yrs; FEV1 pred. 24.9±7.9%) performed up to 15 training sessions within 3 weeks randomised either to Control (CG) or RT (RTG) groups. They were evaluated on the 2nd day of hospitalization, at hospital discharge and after 30 days. Chronic respiratory questionnaire (CRQ), and inflammatory biomarkers (hsCRP, TNF-α, IL-6, IL-8) were evaluated before and 12 week after hospital discharge.

Results: CT as well as IT can significantly improve exercise capacity in pre-LTx patients. IT seems to be better tolerated, expressed by a lower grade of dyspnoea and significantly better feasibility of the exercise protocol.

In conclusion, vitamin D deficiency was significantly associated with higher drop out rates from PR and there was a tendency towards a poorer improvement in E SWT.

1892 Vitamin D status in patients with COPD who participate in pulmonary rehabilitation (PR): Characteristics and effects of PR

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Purpose: This study was conducted to investigate the effect of nutritional support using whey protein-rich supplement which has an anti-inflammatory effect on exercise performance and QOL, and systemic inflammation in stable COPD.

Methods: Thirty-six patients with stable COPD (mean (SD) age 77.2±5.8yrs, FVC 2.70±0.72L, FEV1 1.10±0.44L, predicted PEV 44.5 (16.2%)), FEV1/FVC 44.5 (16.9%) were studied. COPD patients under continuing pulmonary rehabilitation (PR) were randomly divided into a nutrition group and a control group (education only). In nutrition group whey protein-rich supplement (400 kcal/day) was supplied for 12 weeks. Whey protein, a protein complex derived from milk, has been shown to have a strong anti-inflammatory effect in vitro. PR program consisted of respiratory muscle (RM) stretch gymnastics, RM training, breathing retraining, 3-week wall mobilization, and chair exercise. Lung functions, six-minute walking distance (6MWD), chronic respiratory questionnaire (CRQ), and inflammatory biomarkers (hsCRP, TNFα, IL-6, IL-8) were evaluated before and 12 week after nutritional intervention.

Results: In the nutrition group, inflammatory markers decreased significantly (hsCRP, 2.7 (3.4) vs 1.5 (2.0)mg/L (p<0.001), TNFα, 1.2 (0.4) vs 1.2 (0.4)pg/ml, IL-6, 2.7 (4.1) vs 2.2 (1.1), IL-8, 2.0 (1.3) vs 1.1 (1.1)pg/ml (p<0.01)). 6MWD increased significantly from 322 (183) to 368 (182)m (p<0.01). The total values of CRQ also increased from 103 (16) to 109 (17).

Conclusions: We conclude that anti-inflammatory nutritional support using whey protein-rich supplement might enhance exercise capacity and QOL in stable COPD by improving systemic inflammation.
Tuberculin skin testing (TST) may be compromised by immunodeficiency. We performed direct comparisons between tests in immunocompromised patients.

Background: The incidence of tuberculosis (TB) in The Netherlands is partly driven by disease progression of unidentified TB infection (LTBI) in immigrants. Screening newly arriving immigrants for LTBI with the Quantiferonγ2 Gold In-Tube (QFT-GIT) might be a promising intervention.

Aims and objectives: To estimate the risk for progression to active tuberculosis within two years of entry in newly arriving immigrants with a positive QFT-GIT response.

Methods: In a case-based design, we determined the prevalence of positive QFT-GIT responses among a random sample of 1375 immigrants newly arrived during 2009-2011 (the base). Active tuberculosis patients (cases) within two years after entry were extracted from the Netherlands Tuberculosis Register from a cohort of immigrants arriving in 2006. We assumed a QFT-GIT sensitivity of 90% and no tuberculosis transmission occurred after entry.

Results: Among the 1369 immigrants with valid QFT-GIT responses, overall 20% were positive. Stratified by low (<100/100,000), middle (100-200/100,000) and high (>200/100,000) tuberculosis incidences in person’s region of origin, QFT-GIT positivity was 16%, 24% and 26%, respectively. The risk for progression to disease per 100,000 newly arriving immigrants from low, middle and high incidence regions was 347 (95% CI: 75-1185), 398 (86-1355), and 801 (132-2942), respectively, if QFT-GIT positive, compared to a risk of disease of 7 (0-113), 14 (0-212), and 31 (0-491) per 100,000 if QFT-GIT negative.

Conclusion: Newly arriving immigrants with a positive QFT-GIT response have a significant risk of progression to TB within two years of entry, even immigrants from low incidence regions. QFT-GIT offers added-value in the immigration screening program.

The superior sensitivity of IFNy release assays (IGRAs) in diagnosing LTBI above tuberculin skin testing (TST) may be compromised by immunodeficiency. We performed direct comparisons between tests in immunocompromised patients.

IGRAs (T-SPOT/QFT) and TST were performed on clinical data on drugs and TB exposure were collected. Interim results from 193 organ transplant patients and 204 patients with rheumatoid arthritis (RA) are presented.

In transplant patients, 80% had results for all 3 tests, which were less often positive for TST (11.7%) than for T-SPOT (20.8%) and QFT (15.6%, p = 0.018). Agreement was substantial between IGRAs (κ=0.61), and only fair between IGRAs and TST (κ=0.22, T-SPOT; 0.34, QFT). All 3 tests were more often negative despite TB risk factors in patients <1 year post transplant as compared to patients ≥1 year. In RA patients, 91% had result for all 3 tests, which were positive in 36.9% (TST), 26.3% (T-SPOT), and 24.2% (QFT, p<0.001). Agreement was only fair between IGRAs and TST (κ=0.29, T-SPOT; 0.33, QFT) and substantial between IGRAs (κ=0.77). The correlation between QFT and TST was 0.93. The Area Under the ROC curve was comparable 0.89-0.91 for both. The correlation between filter paper and plasma IP-10 was very high (r=0.93). The Area Under the ROC curve was comparable 0.89-0.91 for both IP-10 tests and IFNy and the 3 tests had comparable sensitivity and specificity 74.7%, 78.1% and 100%, respectively (and n.s. differences).

Conclusion: Plasma from M.tb. antigen stimulated blood can be dried on filter paper and transported over long distances at ambient temperature before analysis. Compared to the currently available TST, the filter paper assay allows for high throughput centralized analysis, and could increase the dissemination of specific tests for LTBI in resource restraint settings where IGRAs as we know them today are too complicated to do.
1899

Bifunctional T cells allow for discrimination between latent and active tuberculosis

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Introduction: The diagnosis of active tuberculosis remains challenging especially in a high tuberculosis incidence country as South Africa. We propose that further knowledge on the Mycobacterium tuberculosis (MtB)-specific bifunctional cytokine immune response will help to immunologically distinguish latent versus active disease.

Material and methods: Tuberculosis was diagnosed by culture positivity. Latent tuberculosis was confirmed by a tuberculin skin test on people who did not have clinical symptoms of active tuberculosis. Following informed consent, peripheral blood was drawn from 12 persons with active and 12 persons with latent tuberculosis. To compare the MtB-specific immune response, 200 000 mononuclear cells/well were stimulated with the MtB-specific antigens ESA16/CFTP10, MTP65 and PPD overnight and Interferon gamma (IFNg), Interleukin (IL)-2 or IFNg/IL-2 producing T cells were detected as spot forming cells in a FluorSpot plate.

Results: As expected, MtB-specific IFNg immune response did not discriminate between active and latent tuberculosis. In contrast persons with latent tuberculosis had significantly higher numbers of MTP65-specific cells producing IL-2 (p=0.0235) and bifunctional cells producing IFNg/IL-2 (p=0.03). Furthermore an algorithm using the ESA16/CFTP10 induced IFNg, IL-2 and double positive cells significantly distinguished between the two cohorts (p=0.001).

Conclusion: These preliminary data reveal that defining effector and central memory T cells might allow a better differentiation between latent and active tuberculosis in a blood cell test even in a high incidence country. This is an ongoing study.

1900

IP-10 measurement using a point of care test for the diagnosis of active tuberculosis

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Introduction: Measurement of IP-10 released by whole blood stimulation with tuberculosis (TB) specific antigens has recently been proposed as a new tool for the diagnosis of tuberculosis (TB) with a sensitivity (SE) similar to that of the Quantiferon TB in tube-assay (QFT, Cellestis). More data is needed on the 81 patients. IP-10 was measured by using a multiplex assay (MPA, Biorad) and IP-10 LFI. Pearson correlation for IP-10 measurements by MPA and LFI was 0.53 (95%CI 0.3-0.76), 70% for IP-10 MPA (19/25; CI 0.55-0.9) and 63% for IP-10 LFI (95%CI 0.3-0.7). The SE in patients with active TB was 56% for QFT (14/25, CI 0.35-0.76), 70% for IP-10 MPA (18/25; CI 0.55-0.9) and 63% for IP-10 LFI (95%CI 0.3-0.7).

Conclusion: Smoking increases the risk of having a false negative or indeterminate IGRA results. IGRA test results should be interpreted with care in smokers.

1901

Methylated HBHA produced in M. smegmatis discriminates between active and non-active TB disease among the QFT-IT-responders

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Background: Challenge in tuberculosis (TB) research is to develop a test to distinguish, among the responders to an IFN-γ release assay (IGRA), those who control M. tuberculosis (MtB) replication from those that cannot. IFN-γ response to the Heparin-binding-hemagglutinin (HBHA) of MtB has been associated with latent TB infection (LTBI), but the cumbersome procedures to purify the methylated and immunological active form of the protein from MtB or MtB BCG have prevented the implementation of a diagnostic test. Aim of this study was to evaluate the IFN-γ response to methylated HBHA of MtB produced in M. smegmatis (rHBHAs) in subjects at different stages of TB who scored positive to QuantiFERON-TB Gold in-tube (QFT-IT).

Methodology/Principal findings: 87 subjects at different stages of TB who scored positive to QFT-IT were selected. IFN-γ response to in vitro whole blood stimulation with rHBHAs was evaluated by short-term and long-term tests and detected by ELISA or flow cytometry. We demonstrated that the IFN-γ response to rHBHAs is mediated by CD4+ T-cells with an effector-memory phenotype. This response, evaluated also by short-term-tests is significantly lower in active TB than in remote LTBI (p=0.0010), past TB (p=0.0152) and recent infection (p=0.05). These results were confirmed by long-term-tests and by qualitative analysis using ROC analysis.

Conclusions: For the first time to our knowledge, we showed that the T-cell response to a recombinant and methylated HBHA of MtB produced in M. smegmatis is a new candidate test to immunologically discriminate between active and non-active TB disease among those responsive to QFT-IT.

238. The burden of work-related respiratory disease: known and new end-points

1902

Occupational exposures and airway obstruction in the burden of obstructive lung disease (BOLD) study

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Introduction: Occupational exposures are a recognised cause of respiratory morbidity but there are few population based estimates of their effects on lung function.

Methods: The Burden of Obstructive Lung Disease programme undertook post-bronchodilator spirometry in representative samples of people over the age of 40 years in 15 sites (N=14,400). It also collected information on occupation, including employment in specific industries, with the length of employment in each. Named industries were classified into three exposure groups: Fumes (F), Inorganic dusts (ID) and Organic dusts (OD). Odds ratios were estimated compared with the unexposed population adjusting for sex, age, smoking, pack-years, height and education, first for any exposure and then for length of exposure. Meta-analytical methods were used to combine risks between sites. COPD was defined as a FEV1/FVC ratio < Lower Limit of Normal.

Results: 10% were exposed to F, 9% to ID and 24% to OD. COPD was more common in those exposed; (OR (95%CI)) for F=1.80 (1.29, 2.53), for ID=1.51 (1.03, 2.22) and for OD=1.27 (0.96, 1.69). However much of the excess risk was seen in those exposed for less than a year. The OR (95%CI) of ten years exposure after the first year were F: 1.03 (0.87, 1.21), ID: 1.00 (0.75, 1.07); OD: 1.06 (0.94, 1.20). After stratification the estimated OR from OD in non-smokers was 1.26 (0.97, 1.64) per 10 years exposure.

Conclusions: Estimates of effects were probably strongly influenced by a healthy worker effect. Further data are needed and are being collected.
1903

Occupational exposure to dusts, gases, and fumes and incidence of COPD in SAPALDA

Amar Mehta1,2, David Miedinger1,2, Robert Bettschart1, Andreas Bircher6, Pierre-Olivier Briveaux1, Ivan Curjic1,2, Hans Krohnmööt1, Nicole Probst-Hensch1,2, Thomas Rothe1, Erich W. Russi1,2, Tamborlane Samaranayake1, Christian Schindler1,2, Irmeli Lindström1,2, Roel Vermeulen5, Thierry Rochat5, Nino Kuenzli1,2.

Conclusion:

The results indicate an association between maternal occupational exposure to LMW/irritant agents and asthma in the child during pregnancy (18.6%). Adj. logistic regression analysis showed an association between maternal occupational exposure to LMW/irritants and asthma in the child (OR 1.11 (95% CI 1.01-1.23)). The same tendency was seen for BMW (OR 1.12 (0.85-1.47)). Adjusted models included: Mothers age, BMI, atopy, use of medication, pets, SGA and gender. Stratifying for atopic status in the children did not change the results: OR 1.21 (0.75-1.96), OR 1.08 (0.77-1.50) for atopic and non-atopic children respectively in the HMW group, and OR 1.13 (0.94-1.35) and 1.13 (1.00-1.27) in the LMW/irritants group. No significant associations to asthma were seen in the other exposure groups.

Conclusion: The results indicate an association between maternal occupational work exposures and the risk of asthma in the child at age 7 years.

1907

Risk factors for decreased work ability among middle-aged men having asthma from youths

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Background:

Occupational exposure to irritants and dusts has shown to contribute to respiratory work disability (Toren et al Thorax 2009;64(4):339-44).

Monday, September 26th 2011
Aims: We studied the effect of asthma which begins in youth on work ability in men around the age of 40, and analysed the risk factors for asthma-related work disability.

Methods: Finnish Defence Force registers in 1986-1990 were used to select: 1. conscripts with asthma representing a mild asthma group (n=485), 2. asthmatics who were exempted from military service representing a moderate/severe asthma group (n=393) and 3. a control group (n=1500) without asthma. 54% of the men in the first asthma group, 44% of the men in the second asthma group and 44% of the controls answered the questionnaire in spring 2009. The coded occupational histories was matched with the asthma-specific Job Exposure Matrix in order to evaluate occupational exposure to asthmogens and respiratory irritants. Logistic regression analyses were used when examining the associations between risk factors and decreased work ability.

Results: Self-assessed current work ability compared with lifetime best in scale 0-10 was decreased (<8) in 28.9% of the first asthma group, in 31.1% of the second asthma group, and in 19.7% of the controls (p=0.007). Current smoking (OR 2.5), being a manual worker (OR 2.7), exposure to irritants (OR 1.7) and abnormal temperatures (OR 1.7) and current severe asthma (OR 3.8) associated with decreased work ability among the asthmatics.

Conclusions: The reduction of work ability in men having asthma from youth may be partly preventable, if young asthmatics are advised to avoid work involving exposure to the irritants or abnormal temperatures and smoking.

239. Surgery for lung cancer: pre-operative evaluation and results

1908 Late-breaking abstract: The impact of extended cervical mediastinoscopy in staging of left lung carcinoma

Adnan Sayar1, Necati Çitak1, Sibel Bıyıklıkale1, Murzaffer Metin1.

Background: Extended cervical mediastinoscopy (ECM) is a method used for staging non-small cell lung cancer (NSCLC).

Methods: Between 1998 and 2011, 159 patients underwent ECM who had left NSCLC, were retrospectively analyzed. If the N2 was limited to the paratracheal or subcarinal spaces without infiltrating the paraortic or subaortic spaces, these cases excluded from the study (negative cases of ECM and positive cases of SCM). Patients who had been reported as cN0 by mediastinoscopy were operated; 64 lobectomies, 43 pneumonectomies, 16 exploratory thoracotomies. The pathological examination of the mediastinal lymphadenectomies revealed APW lymph node metastasis in 36 patients (22.6%) (96.2%) (#5 and #6 sampling in 82 patients, #5 or #6 sampling in 71 patients).

Mediastinal lymph node metastasis was observed in 26 of these patients (true-positive of ECM), remaining 10 patients who had mediastinal lymph nodes metastasis that could be accessed only via SCM were excluded. 123 patients who identified as cN0 by mediastinoscopy were operated; 64 lobectomies, 43 pneumonectomies, 16 exploratory thoracotomies. The pathological examination of the mediastinal lymphadenectomies revealed APW lymph node metastases in 11 patients (false-negative of ECM). Sensitivity, NPV and accuracy of ECM were calculated as 0.70, 0.91, and 0.92, respectively.

Conclusions: ECM has an adequate NPV and accuracy in determining metastases to the APW lymph nodes in patients with left NSCLC.

1909 Improvements in lung cancer surgery

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Background: Recent trends in outcomes of lung cancer treatment might challenge recommendations for acceptable care.


Results: A total of 2201 patients were operated on during the study periods. Surgery was performed at 24 hospitals during the first two periods and at 13 in the last. Resection rates varied among counties from 7% to 31%. From the first to the last period, national resection rates increased from 16% to 19% (p for trend=0.001) and one-year survival increased from 73% to 82%. The proportion of resected patients in pStage I-II decreased from 87% to 83% (p for trend=0.048), the proportion of pneumonectomies from 27% to 15% (p for trend<0.001) and the mortality rate within 30 days of the surgery from 4.8% to 3.0% (p for trend=0.072). In the first two periods, 31% of these early deaths were caused by surgical complications, whereas in the latter period none were. The only unfavorable trend observed was the waiting time from the final diagnostic procedure to surgery, which increased from 29 to 40 days throughout the periods (p<0.001).

Conclusions: Important aspects of lung cancer surgery have improved in recent years and the recommendations for certain quality indicators are challenged. The most important is that the resection rates should be further increased towards a putative optimum exceeding 25%.

1910 Role of thoracoscore (thoracic surgery scoring system) in clinical practice

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Introduction: Thoracic surgery scoring system (Thoracoscore) a multivariate score with 9 parameters, may predict mortality after thoracic surgery (Lim E. et al. Thorax 2010;65;ii:ii27). Its role to assess patient fitness for surgery is not clear.

Cardiopulmonary exercise test (CPEX) is recommended by ERS to assess fitness for radical therapy in lung cancer patients (Brunelli A. et al. Eur Respir J 2009;34:17-41)

Objective: To evaluate role of thoracoscore in patients considered for thoracic surgery.

Methods: Retrospective data analysis of patients investigated for thoracic surgery. Results: Over a 2 period, 22 patients with borderline lung function had CPEX to assess for lung resection. Based on CPEX results, patients were classified into three groups: 1. marginal (true-positive of ECM), 2. acceptable (false-negative of ECM). The only unfavorable trend observed was the mortality in the first asthma group, 44% of the men in the second asthma group, and 44% of the controls answered the questionnaire in spring 2009. The coded occupational histories was matched with the asthma-specific Job Exposure Matrix in order to evaluate occupational exposure to asthmogens and respiratory irritants. Logistic regression analyses were used when examining the associations between risk factors and decreased work ability.

Results: Self-assessed current work ability compared with lifetime best in scale 0-10 was decreased (<8) in 28.9% of the first asthma group, in 31.1% of the second asthma group, and in 19.7% of the controls (p=0.007). Current smoking (OR 2.5), being a manual worker (OR 2.7), exposure to irritants (OR 1.7) and abnormal temperatures (OR 1.7) and current severe asthma (OR 3.8) associated with decreased work ability among the asthmatics.

Conclusions: The reduction of work ability in men having asthma from youth may be partly preventable, if young asthmatics are advised to avoid work involving exposure to the irritants or abnormal temperatures and smoking.

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Adnan Sayar1, Necati Çitak1, Sibel Bıyıklıkale1, Murzaffer Metin1.

Background: Extended cervical mediastinoscopy (ECM) is a method used for staging non-small cell lung cancer (NSCLC).

Methods: Between 1998 and 2011, 159 patients underwent ECM who had left NSCLC, were retrospectively analyzed. If the N2 was limited to the paratracheal or subcarinal spaces without infiltrating the paraortic or subaortic spaces, these cases excluded from the study (negative cases of ECM and positive cases of SCM). Patients who had been reported as cN0 by mediastinoscopy were operated; 64 lobectomies, 43 pneumonectomies, 16 exploratory thoracotomies. The pathological examination of the mediastinal lymphadenectomies revealed APW lymph node metastases in 36 patients (22.6%) (96.2%) (#5 and #6 sampling in 82 patients, #5 or #6 sampling in 71 patients). Mediastinal lymph node metastasis was observed in 26 of these patients (true-positive of ECM), remaining 10 patients who had mediastinal lymph nodes metastasis that could be accessed only via SCM were excluded. 123 patients who identified as cN0 by mediastinoscopy were operated; 64 lobectomies, 43 pneumonectomies, 16 exploratory thoracotomies. The pathological examination of the mediastinal lymphadenectomies revealed APW lymph node metastases in 11 patients (false-negative of ECM). Sensitivity, NPV and accuracy of ECM were calculated as 0.70, 0.91, and 0.92, respectively.

Conclusions: ECM has an adequate NPV and accuracy in determining metastases to the APW lymph nodes in patients with left NSCLC.

1909 Improvements in lung cancer surgery

Trond-Eirik Strand1, Kristian Bartnes2, Hans Rostad1. 1Department of Clinical and Registry-Based Research, Cancer Registry of Norway, Oslo, Norway; 2Department of Cardiothoracic and Vascular Surgery, University Hospital North Norway, Tromsø, Norway

Background: Recent trends in outcomes of lung cancer treatment might challenge recommendations for acceptable care.


Results: A total of 2201 patients were operated on during the study periods. Surgery was performed at 24 hospitals during the first two periods and at 13 in the last. Resection rates varied among counties from 7% to 31%. From the first to the last period, national resection rates increased from 16% to 19% (p for trend=0.001) and one-year survival increased from 73% to 82%. The proportion of resected patients in pStage I-II decreased from 87% to 83% (p for trend=0.048), the proportion of pneumonectomies from 27% to 15% (p for trend<0.001) and the mortality
1912
Timed stair climbing to 20 m altitude identifies lung resection candidates with high exercise capacity
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Background: Clinical evaluation for lung resection includes assessment of pulmonary function and maximum oxygen uptake (VO2max). A VO2max of 20ml/kg/min is considered sufficient for pneumonectomy. Stair climbing as a low-cost alternative to formal treadmill cardiopulmonary exercise testing (CPET), is attractive but lacks standardisation.

Methods: We asked 40 lung resection candidates (bronchiectasis or aspergillosis, n=26; lung cancer, n=7; iatrogenic cyst, n=2), with VO2max <20ml/kg/min, predicted (mean age: 43.7y; mean FEV1: 49.7%; mean DLCOc: 56.9%; 30 pts <70%) to climb to a maximum of 20m elevation as high and as fast as they could. Time of ascent to 20m and elevation reached were measured. Mean VO2 achieved during stair climbing and CPET were compared (MetaMax II, Cortex, Germany).

Results: Mean VO2 was 17.2ml/min. Mean peak VO2 during stair climbing was very similar to that during CPET (23.5 ± 23.6ml/min/kg, p=0.87). Twenty-four patients (60%) reached 20m. There was a good linear correlation between speed of ascent and peak VO2 (r=0.63 for stair climbing and 0.67 for CPET), but 4 of those patients (17%) remained below a peak VO2 of 20ml/kg/min. However, all 16 patients (67%) who reached 20m and climbed with a speed of >15min/m had a VO2 peak of >20ml/min/kg during stair climbing and CPET. No patient with a FEV1 <40% could climb to 20m or ascend faster than >15min/m.

Conclusions: Speed of ascent of >15min/m accurately identifies patients with a peak VO2 of >20ml/min/kg, thereby obviating the need for CPET in those patients.

1913
Prediction of postoperative FEV1 and chronic dyspnoea using quantitative computed tomography (CT) in lung resection candidates
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Aim: Preoperative evaluation of lung function before lung resection is necessary in order to avoid postoperative morbidity. The aim of the study is to evaluate the role of quantitative CT in predicting postoperative FEV1 and patient's chronic dyspnoea.

Methods: Twenty-eight patients with non-small cell lung cancer have been evaluated. Lung function tests (LFTs) and chest CT scan were performed preoperatively. Fifteen patients (group A) had normal LFTs, thirteen patients (group B) had impaired lung function, requiring further testing. Quantitative evaluation of CT using dual threshold (-910 up to -500 Hounsfield Units) estimated total functional lung volume and the volume of the lobe(s) to be resected. Postoperative FEV1 was predicted by reducing the postoperative value by the same fraction that the resected part contributed to the total lung volume, in both groups. Postoperative LFTs were performed 3 months after surgery. Postoperative dyspnoea was evaluated using the modified Medical Research Council (mMRC) scale.

Results: The postoperative predicted and postoperative actual values of FEV1 were significantly correlated in both groups (Group A: r=0.897, p<0.0001, Group B: r=0.940, p<0.0001). Predicted volume loss as a percentage of total lung volume correlated significantly with postoperative mMRC (r=0.647, p<0.001).

Conclusion: Quantitative CT in patients undergoing lung resection appears to be a useful tool in evaluating postoperative patient’s status as it predicts postoperative FEV1 and postoperative mMRC.

1914
FEV1 is not a prognostic marker in operated patients with stage I or II non-small cell lung cancer (NSCLC)
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Background: In retrospective studies lung cancer mortality was found to be higher in patients with chronic obstructive pulmonary disease (COPD), defined as a FEV1 <70% of the predictive value. In the Cher®Nostril and the Paccora trials, based on patients with unresectable clinical stage III, a strong relationship was observed between FEV1 and overall survival (OS). In a smaller study, FEV1 was a prognostic factor for OS in operated patients (Nakajima et al. Thor Cardiovasc Surg 2009;57:339-342).

In our study we investigated whether the presence of COPD is a prognostic marker in patients with resectable stage I and II NSCLC.

Methods: All relevant clinical information was gathered retrospectively from 77 patients undergoing complete resection without preoperative chemoradiotherapy between January 2003 and January 2006. All patients were staged according to the 7th TNM-classification. Primary endpoints were OS and progression-free survival (PFS). Follow-up information was complete for all patients and ended in July 2010. Patients were classified as having a FEV1 <70% or a FEV1 >70%.

Results: According to the Kaplan Meier analysis (log rank test) FEV1 was not a significant prognostic factor for OS (log=0.461) or PFS (log=-0.530). In a Cox multiple regression analysis the adjusted hazard ratio for FEV1 (measured on a continuous scale) was 1.632 (p=0.458) after adjustment for stage and age.

Conclusion: In contrast to other studies our data show that FEV1 is not a prognostic factor in patients with resectable stage I and II NSCLC. Precise selection criteria regarding cardiopulmonary function excluding patients with a very poor cardiopulmonary function, could be responsible for this finding.

1915
Lobectomy tolerance in COPD patients
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Lung cancer is often associated with COPD. COPD patients have higher postoperative morbidity and mortality because of low respiratory reserve. Morbidity and mortality in these patients amounts to 60% and 10-14% respectively (Seikone Y., 2001, Subotic D., 2007). To investigate factors influencing the risk of postoperative morbidity and mortality and to determine criteria for lobectomy intolerance in COPD patients.

Material and methods: 279 patients underwent lobectomy from 2001 to 2008 were included in a retrospective study. Mean age was 61±12, male/female ratio = 204/75. Patients were divided in three groups according to recommendation of GOLD 2007. Group 1 – 154 non-COPD patients, group 2 – 47 patients with mild COPD and group 3 – 78 patients with moderate to severe COPD. Comorbidity of the patients was assessed by using of Charlson comorbidity index (CCI).

Results: Morbidity and mortality were found to be increased in patients with more severe obstruction. Thus morbidity was 32% in nonCOPD patients, 34% - with mild COPD and 46% - with moderate to severe one. Mortality was 3.9, 8.5 and 12.8% respectively. However multivariate analysis showed that severity of COPD and predicted postoperative FEV1 were not independent factors of morbidity and mortality.

Morbidity in patients with ppoFEV1 < 40% was 5%, whereas it was 7% in group with ppoFEV1≥40%.

CCI was found to be the only independent risk factor. Morbidity in patients with CCI ≥ 6 was 100%. Combination of CCI ≥ 6 and ppoFEV1 < 50% was accompanied by very high risk of mortality (mounted 70%).

Conclusion: ppoFEV1 < 40% is not independent criterion of lobectomy intolerance in COPD patients. Significant factor of functional inoperability is combination of CCI ≥ 6 and ppoFEV1 < 50%.

240. Resuscitation and ventilation in the baby and infant

1916
Neonatal resuscitation at the community level
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Introduction: Community Based New Born Care Program (CB-NCP) was piloted
in Nepal in order to reach the MDG 4 target, which focuses on decreasing the perinatal mortality. The program focuses the community level and reaches the local doctors, community level health workers and volunteers, educates and trains them with major emphasis to correctly identify and manage birth asphyxia by the use of DeLee suction and bag and mask ventilation.

Aims: The aim of this study was to assess the knowledge and proficiency gained by the community level (VHW/MCHW, FCHV) and health facility level health workers who participated in a Community Based New Born Care training program.

Methods: Based on CB-NCP curriculum designed by the Child Health Division, two questionnaires were developed for all levels of knowledge of the 57 health facility staffs including doctors, 36 VHW/MCHW and 141 FCHV were collected through semi-structure questionnaire and the skill was assessed through the observational checklist with practical hands on bag and mask ventilation in a neonatal manikin.

Results: The knowledge of health workers, VHW/MCHW and FCHV regarding the management of birth asphyxiated baby was 100% (N=57/57), 94% (N=34/36) and 90.8% (N=126/141) respectively. The knowledge of FCHV regarding the management of asphyxiated new born was comparatively less than Health Worker and VHW/MCHW. Similarly, 49.1% (N=26/57) health workers, 50% (N=18/36) VHW/MCHW and 100% (N=141/141) FCHV correctly demonstrated the skills of management of asphyxiated newborn.

Conclusions: Further studies are required to finally confirm the effectiveness of the intervention at the community level before implementing the program in other districts.

1917 The influence of oxygen inflow on ventilatory parameters during manual ventilation
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Background: Despite of self-inflating bags (SIB) widespread use, studies have concluded that many factors may have influence on ventilation.

Aim: To evaluate and to compare ventilatory parameters during manual ventilation with 4 different oxygen flows attached to the SIB.

Methods: Two different physiotherapists were asked to ventilate 2 lung models (neonatal/pediatric) using 3 SIBs (Hudson®, Laerdal®, IG-Meyer®) with 5, 10, 15 and 15L/min of oxygen inflow attached. A lung function monitor (CO2SMOplus®) recorded inspiratory volume (Vi), peak inspiratory pressure (PIP), peak inspiratory flow (PIP) and expiratory flow (PEF) and inspiratory time (Ti). The oxygen inflows were compared using ANOVA for repeated measures and Tukey’s test with p<0.05 considered statistically significant.

Results: With 4 different SIB brands in neonatal and pediatric models, the oxygen inflows influenced Vi, PIP, PIP, and Ti (<p<0.001). When compared 0 and 15L/min, we found a significant increase in PIP in all neonatal SIB brands. Also, there was a difference in Ti delivered by neonatal Hudson® SIB.

Conclusion: We found great variability in ventilatory parameters depending on the oxygen inflow. The Vi, PIP, PIP, and Ti showed a large variation. Professionals should be aware of those differences and the choice of the oxygen flow used should be taken with caution.

1918 Influence of mask leak on applied volumes and pressures during simulated resuscitation of neonates
Julia C. Hartung, Marcus Kelm, Hendrik Fischer, Gerd Schmalisch, Charles C. Roehr. Neonatology, Charité Universitätsmedizin Berlin, Berlin, Germany

Introduction: Self-inflating (SI) bags and T-piece resuscitators are used for bag and mask ventilation of neonates. Leaks between face and mask occur frequently.

Aim: To examine the preventive effects of moderate (MH) or severe hypercapnia (SH) on BLEO-induced CNLI.

Method: Rabbit pups received BLEO (1 mg/kg/d i.p.) or saline vehicle from postnatal days 1-14 while being exposed to FiCO 2 0.05 (PaCO 2 70 mmHg; MH), FiCO 2 0.07 (PaCO 2 90 mmHg; SH) or normocapnia (NC). Inflammation was assessed by tissue counts of immunoreactive macrophages (CD68) and neutrophils (MPO). PHT was assessed by echo-Doppler measurement of pulmonary vascular resistance (PVR), right ventricle (RV) flecth, pectusepultum (LV-S) weight ratio and percentage medial wall thickness (%SMWT) of pulmonary resistance arteries. Markers of lung development included weight, mean linear intercept, tissue fraction, secondary crest and peripheral vessel counts.

Results: SH, but not MH, attenuated BLEO-induced macrophage influx and prevented PHT, as evidenced by normalized PVR and significantly (p<0.01 vs. BLEO+NC) decreased RV/LV+S and%MWT. Neither SH nor MH affected BLEO-induced neutrophil influx, inhibited lung growth, septal thinning, impaired alveolarization or pruning of peripheral blood vessels.

Conclusions: SH prevented PHT, which we speculate was the result, in major part, of inhibited macrophage influx. Neither influx of neutrophils nor pruning of peripheral arteries appeared to contribute significantly to PHT in BLEO-mediated CNLI. Funded by the CIHR.

1919 Appropriate level of volume targeting for ventilated infants born at or near term
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Aims: To determine the most appropriate level of volume targeting (VT) for ventilated infants born at or near term.

Method: Study one: expiratory tidal volumes (VTe) were measured during time cycled, pressure limited ventilation either using a pneumotachograph or the ventilator’s software; at least 80 breaths were analysed per infant. Study two: two infants were studied at VT levels of 4, 5 and 6 ml/kg delivered in random order, with return to baseline between each VT level. The transpulmonary pressure-time product (PTPdi), a measure of the work of breathing, was assessed at each VT level and during the baseline periods. To measure PTPdi, oesophageal and gastric pressures are measured and PTPdi calculated by integration of the transpulmonary pressure signal with time for each breath and expressed per minute. In both studies, infants are only assessed when their blood gases are within the normal range.

Results: To date: Study one: 20 infants, median gestational age of 39 (range 35-41) weeks, had a median VTe of 5 (range 1.4-9.7) ml/kg; 50% of infants had a VTe outside the “normal” tidal volume range (4 to 6ml/kg). Study two: the median PTPdi of 11 infants, median gestational age 39 (35-41) weeks, at a VT level of 4 ml/kg (310, IQR 242-334 cmH2O/min) was almost double that at 6 ml/kg (median 163, IQR 122-220 cmH2O/min), (p<0.001).

Conclusion: During time cycled, pressure limited ventilation, infants born at or near term are frequently ventilated using volumes outside the “normal” tidal range. Yet, even within that range, low compared to high levels of volume targeting significantly increase the work of breathing.

1920 Therapeutic hypercapnia prevents pulmonary hypertension in rats with bleomycin-induced chronic neonatal lung injury
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Bleomycin (BLEO)-induced chronic neonatal lung injury (CNLI) is characterized by severe inflammation, arrest of lung development and pulmonary hypertension (PHT). To examine the preventive effects of moderate (MH) or severe hypercapnia (SH) on BLEO-induced CNLI.

Methods: Rat pups received BLEO (1 mg/kg/d i.p.) or saline vehicle from postnatal days 1-14 while being exposed to FiCO2 0.05 (PaCO2 70 mmHg; MH), FiCO2 0.07 (PaCO2 90 mmHg; SH) or normocapnia (NC). All infants were studied at VT levels of 4, 5 and 6 ml/kg delivered in random order, with return to baseline between each VT level. The transpulmonary pressure-time product (PTPdi), a measure of the work of breathing, was assessed at each VT level and during the baseline periods. To measure PTPdi, oesophageal and gastric pressures are measured and PTPdi calculated by integration of the transpulmonary pressure signal with time for each breath and expressed per minute. In both studies, infants are only assessed when their blood gases are within the normal range.

Results: To date: Study one: 20 infants, median gestational age of 39 (range 35-41) weeks, had a median VTe of 5 (range 1.4-9.7) ml/kg; 50% of infants had a VTe outside the “normal” tidal volume range (4 to 6ml/kg). Study two: the median PTPdi of 11 infants, median gestational age 39 (35-41) weeks, at a VT level of 4 ml/kg (310, IQR 242-334 cmH2O/min) was almost double that at 6 ml/kg (median 163, IQR 122-220 cmH2O/min), (p<0.001).

Conclusion: During time cycled, pressure limited ventilation, infants born at or near term are frequently ventilated using volumes outside the “normal” tidal range. Yet, even within that range, low compared to high levels of volume targeting significantly increase the work of breathing.

1921 The distribution of lung aeration at different positive end-expiratory pressure levels in newborn rabbits
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Background: Very preterm newborns with respiratory distress at birth demonstrate increased end-expiratory lung volumes when ventilated with positive end-expiratory pressure (PEEP). However, the regional distribution of ventilation is unknown, especially if PEEP is not held constant but altered as occurs during face mask removal.

Aim: To determine the how the distribution of ventilation changes between different PEEP levels.

Method: Rabbit pups (28dGA) were delivered by c-section and mechanically

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ventilated with a peak inflation pressure of 35cmH2O and a sequence of PEEP. The PEEP sequences were (A) 0-5-10-5cmH2O, (B) 0-5-10-0-5cmH2O and (C) 0-5-10-0-10cmH2O. Phase contrast X-ray imaging was used to image and analyse the distribution of aerated lung.

**Results:** In sequence A and B, upper lobes (U) were more aerated than lower lobes (L) at functional residual capacity (FRC) throughout the ventilation period (A: 100PEEP U vs L, 70.9±1.5% vs 58.6±2.8%, p<0.05). Tidal volume (VT) aerated U and L similarly until the volume of the lungs at peak inflation (VPPI) achieved >70% of maximal lung volume (p<0.05). Once VPPI was >70%, VT aerated more than U (A: U vs L: 72.2±3.7% vs 30.3±3.6%, p<0.05; B: U vs L: 20.4±1.6% vs 26.9±1.7%, p<0.05). Sequence C ventilated differently; FRC was only different between lobes at 0PEEP (p<0.05) and VT lacked difference at 100PEEP despite VPPI >70% (p<0.05).

**Conclusion:** At FRC, U are better aerated than L, at different PEEP levels. During inflation, the VT was distributed more to lower lobes than upper lobes after the lungs were over-inflated. This is not observed if lungs were initially aerated with a high PEEP.

**Methods:** 89 patients from 14 sites were randomized to either azithromycin 250 mg daily or placebo, for 12 months. All were reviewed at three-monthly intervals during treatment and at 3 months follow-up. At each review the following were assessed: exacerbation frequency (being the primary endpoint), lung function, qualitative and quantitative sputum bacteriology, serum and sputum inflammatory markers, adverse effects, symptom scores and St George’s respiratory questionnaire. High resolution CT-scans were performed at study entrance and end of study.

**Primary results:** 81 patients completed the study. At the end of 12 months’ treatment the exacerbation group showed a significant reduction in exacerbation frequency as compared to the placebo treated group (1.28/year, SD 1.32 vs 2.67/year, SD 1.95, p<0.001). No significant differences were found with respect to lungfunction, inflammatory markers and adverse effects between groups.

**Conclusions:** Longterm azithromycin treatment significantly reduces exacerbation frequency in patients with non-CF bronchiectasis, without additional side effects.
severities (3-severe and 21-mild cough). Myeloperoxidase (MPO), neutrophil elastase (NE), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α) were measured from spontaneous sputum samples. Multivariable linear regression was used to determine independent factors associated with cough severity (LCQ).

**Result:** 187 completed the study. 58.2% were female. Median age was 65 years. 77.3% had reflux using HCQ.

Reflex ⇒ severe cough symptoms as per LCO (15.2 (3.5) vs 19.4 (1.9), p < 0.001). Sputum levels of MPO, NE, IL-8 and TNF-α were significantly higher in reflux+ve group (p < 0.0001 for all comparisons).

After adjusting for age, gender, co-morbidities, disease severity and chronic colonization, reflux was independent with cough severity (p = 0.27 standard error 0.81, p = 0.0022).

**Conclusion:** The presence of airways reflux is associated with more severe cough and increased airway inflammation in bronchiectasis.

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**1927**

The relationship between airway bacterial load and airways inflammation in stable non-cystic fibrosis bronchiectasis

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**Objective:** To investigate the relationship between airway bacterial load and markers of airways inflammation in stable patients with bronchiectasis.

**Methods:** 302 patients with non-CF bronchiectasis confirmed by HRCT were enrolled. At 6-monthly review, sputum samples were processed to determine bacterial load, expressed as log10 colony forming unit/ml (cfu/ml). Sputum sol was analysed for myeloperoxidase (MPO) and neutrophil elastase (p < 0.001) and tumour necrosis factor alpha (TNF-α) were measured by ELISA.

**Results:** 67 patients (22.1%) of patients grew no pathogens. Pathogenicmicroorganisms were obtained in 77.9% of patients, most frequently *Haemophilus influenzae* (37.4% of isolates). *Pseudomonas aeruginosa* (20.4%), Staphylococcus aureus (13.2%), Streptococcus pneumoniae (11.9%) and Moraxella catarrhalis (10.6%).

Airway inflammation increased progressively with increasing bacterial load. Statistically significant differences were observed, when compared to patients with no pathogens, at bacterial loads above 1 × 10^4 cfu/ml for MPO (p < 0.01), neutrophil elastase activity (p = 0.006) and IL-8 (p = 0.02), and above 1 × 10^5 for TNF-α (p = 0.004) and above 1 × 10^6 for IL-8 (p = 0.003).

**Conclusion:** There is a direct relationship between airway bacterial load and the degree of airway inflammation in stable bronchiectasis.

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**1929**

Safety and efficacy of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis

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**Introduction:** Ciprofloxacin dry powder for inhalation (DPI) uses PulmoSphere™ technology to target the lungs of patients chronically colonized with bacterial pathogens.

**Objective:** This phase II study assessed the efficacy and safety of ciprofloxacin DPI treatment for 28 days in non-cystic fibrosis bronchiectasis (non-CF BE) patients.

**Methods:** Adult patients with pulmonary stable non-CF BE received twice-daily 32.5 mg ciprofloxacin (50 mg ciprofloxacin DPI) or matching placebo for 28 days, with a 56-day follow-up. The primary endpoint was reduction in total bacterial load in sputum at end of treatment (EOT) compared with placebo.

**Results:** The mean baseline characteristics in the intent-to-treat population (N=124) were: age 63, weight 70 kg, FEV1 56% of predicted. At EOT, ciprofloxacin DPI reduced mean bacterial load by 3.6 logs, vs 0.3 logs with placebo (p < 0.0001), and median CRP level was 2.45 mg/l lower compared with placebo (not significant). Mean difference in the St George’s Respiratory Questionnaire at EOT was 3.6 points between treatment arms (p = 0.059). Fewer patients treated with ciprofloxacin DPI than with placebo experienced an exacerbation requiring antibiotic treatment (23% vs 28%, not significant). The adverse event rate was similar in both treatment arms. Very few bronchopneumonias occurred (n=6, 2 after EOT). They were equally distributed between both groups.

**Conclusions:** Ciprofloxacin DPI significantly reduced bacterial load in patients with non-CF BE (p < 0.0001) and was well tolerated. Several secondary endpoints showed a trend in favour of ciprofloxacin DPI. Ciprofloxacin DPI is a promising candidate for investigating benefits of long-term therapy in non-CF BE patients.

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**1930**

Antimicrobial efficacy of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis

Jeff Alder1, Robert Wilson1, Tobias Wele1, Eva Polverino2, Anthony De Soyza3, Hugh Greivelle2, Anne O’Donnell3, Peter Reimnitz4, Barbara Hample8, 1Global Clinical Development, Bayer Healthcare Pharmaceuticals Inc. Montreal, N.D, United States; 2Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom; 3Klinik fuer Pneumologie, Medizinische Hochschule Hannover, Hannover, Germany; 4Servicio de Pneumol., Hospital Clinic i Provincial, Barcelona, Spain; 5Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne, United Kingdom; 6Chest Clinic, Royal Adelaide Hospital, Adelaide, Australia; 7Division of Pulmonary, Critical Care and Sleep Medicine, Georgetown University Hospital, Washington, DC, United States; 8Global Clinical Development, Bayer Schering Pharma AG, Wuppertal, Germany; 9Global Clinical Development Antinfectives, Bayer Schering Pharma AG, Berlin, Germany

**Introduction:** Ciprofloxacin DPI for inhalation (DPI) is a formulation of the anti-Pseudomonal (PulmoSphere™ technology) development for long-term therapy of non-cystic fibrosis bronchiectasis (non-CF BE). This phase II, randomised, double-blind study was designed to assess efficacy and safety over 28 days in non-CF BE patients with positive sputum culture for predefined respiratory pathogens (RP).s

**Methods:** Adult patients with non-CF BE received 25.2 mg ciprofloxacin (50 mg ciprofloxacin DPI) or matching placebo bid for 28 days, with a 56-day follow-up. The primary endpoint was reduction in total bacterial load in sputum at end of treatment.
of treatment (EOT). In addition, eradication of RPs and reduction of individual species was documented.

Results: The primary endpoint of significant reduction in bacterial load of RPs at EOT was achieved (log₃ -3.6 < -0.3 for placebo, p<0.001). In addition, greater reductions and eradication were achieved for the major pathogenic species including, Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pneumoniae. The eradication rates for the baseline pathogens at EOT were 35% vs 8% for placebo. At EOT, eradication was achieved in all patients infected at baseline with M. catarrhalis and in all but 1 patient infected with H. influenzae.

Conclusions: Ciprofloxacin DPI achieved a significantly greater reduction in total bacterial burden than placebo. A promising trend in reduction and eradication of the major pathogenic species was also noted. Ciprofloxacin DPI has demonstrated promise for long-term inhalation therapy to reduce the major pathogenic species in non-CF BE, which could reduce the incidence of exacerbations.

242. Tuberculosis in immunocompromised hosts

P1931
HIV/ TB in Belarus
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Understanding the key role which HIV infection plays in deteriorating TB epidemic situation is crucial for implementing HIV/TB collaborating activities in the Belarusian health care system.

The following trends on TB and HIV incidence were reported during the last eight years (2002 – 2009) in Belarus: 10% decrease in TB incidence from 5 139 to 4 633 with the 17% increase in HIV incidence from 915 to 1072; and dramatic (7.5 fold) increase in TB/HIV co-infection incidence from 35 up to 265. The following trends in HIV mortality has been observed in these years: 24 cases in 2002 and 223 cases (9.3 fold increase in 2003). In the reasons of death for HIV positive patients only 4 (16.7%) patients of all HIV patients died of TB in 2002 to compare with 123 (55.2%) of HIV patients died of TB in 2009. The following social structure of the patients with HIV/TB co-infection has been reported: intravenous drug users (63.4%), heavy drinkers/alcohol addicts (26.8%), patients with history of imprisonment (40.9%), and unemployed (67.1%). Gomel region is the most TB/HIV affected Belarus region, where 61.1% of cases were concentrated of all registered TB/HIV in the country (01.10.2010).

In order to control TB/HIV co-infection spread specific measures based on close cooperation between TB and HIV programs has been implemented in Belarus including: TB prevention, early diagnosis and adequate treatment of TB in HIV positive population.

P1932
Experience from implementation of collaborative TB/HIV activities in Republic of Macedonia – Where did we go wrong and where do we go from here?
Dance Gadeva Nikolovskav1, Stefan Talevski2, Hristijan Jankuloski3. 1Project Implementation Unit, GFATM Funded Program for TB Control, Ministry of Health, Skopje, Macedonia, The Former Yugoslav Republic of; 2Intensive Care, Skopje University, Skopje, Macedonia, The Former Yugoslav Republic of; 3High Risk Groups, NGO Healthy Options Project Skopje, Skopje, Macedonia, The Former Yugoslav Republic of

Since 2004, Republic of Macedonia has implemented 3 GFATM funded grants. RM is the lowest HIV prevalence country in the SEE Region; the cumulative total number by the end of 2010 is 134, and the number of new TB cases in 2010 was 420. To date, 4 cases were diagnosed with HIV and TB.

To analyze joint HIV/TB activities in the past 6 years, identify gaps and challenges to be addressed in order to provide recommendations for policy makers.

We have performed desk analysis of reports on joint HIV/TB activities performed in the period 2004-2010, submitted to GFATM.

NGO HOPS delivers TB prevention education for high-risk groups - IDUs, psychiatric patients, Roma, refugees/asylum seekers and PHLIV. By the end of 2010, total of 7025 HRG representatives have been educated for TB, representing an extraordinary collaboration between the Government and NGO sector.

Voluntary and Confidential Counseling and Testing (VCC&T) services are offered to TB patients at Lung Diseases Institute, by one trained nurse. Analyzed quarterly, the results vary significantly, ranging from 0% tested to as high as 75% tested for some of the cohorts.

Although RM has shown significant achievements in implementation of GFATM funded programs for TB and HIV/AIDS, there is still lot of work to combine services and address prevention. There is a need to expand VCC&T countrywide, scale-up activities as to include other HRG (e.g. sex workers) and necessity for capacity building of communities to address TB in PHLIV. In addition, we have to still work to strengthen institutional support for coordinated response and involve clients in development of relevant strategies.

P1933
Bacteriological profile in new cases of TB-HIV coinfected patients in Romania
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Background: Tuberculosis and HIV infection are two serious problems, which associated condition is one another negative. In Romania there is an increased prevalence of tuberculosis, but proportion of TB-HIV coinfected patients remains low. Due to management issues in this group of patients, bacteriological identification and susceptibility profile are very important.

Aims: To identify the bacteriological profile of strains isolated from new cases of TB-HIV patients and to evaluate the management in this group of patients.

Methods: Descriptive retrospective analysis of new cases of TB-HIV coinfected patients reported in 2009 in the National Register of Tuberculosis.

Results: Were analyzed 155 patients (70.8%) representing the new cases from a total of 219 TB patients notified as seropositive. The mean age was 28 years, 68.3% males, most of them with pulmonary TB (127 patients, representing 81.9% of total cases). Bacterial confirmation rate in culture was low (48.3%), even in pulmonary TB cases (69 patients). Drug resistance was certified in six cases: monoresistance to rifampicin in one case and MDR in 5 cases. Among the patients of our group 114 were successfully treated, 10 patients abandoned TB treatment and 6 failed. The mortality rate was 11.6% (18 patients), most of deceased in pulmonary TB cases (8,33%).

Conclusions: We found a low rate of drug resistance in our group, but bacteriological confirmation was possible only in 48.3% cases. Intensified efforts in bacteriological examinations are necessary to confirm the TB in HIV patients and to exclude other pathology, for a appropriate management.

P1934
Multidrug-resistant tuberculosis (MDR-TB) and HIV co-infection in Romania
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Background: Although Romania is a country with high TB notification rate, the weight of HIV-positive patients among all TB cases is around 1%. Besides, the MDR-TB and HIV co-infected cases are only a few yearly, but they have very low chance to be successfully treated.

Aims: To analyze treatment outcomes of MDR-TB and HIV co-infected patients reported in Romania, from 2006 to 2009.

Methods: Descriptive retrospective analysis of MDR-TB HIV co infected patients reported between 2006-2009 in the TB National Electronic Database.

Results: A total of 23 such cases have been notified in those 4 years. All were under 50 years old (13 even under 21 years). Gender ratio was F/M = 10/13. Only 20 patients were on antiretroviral therapy. All had pulmonary TB. As case category 11 were new cases, 3 relapses, 3 chronics, 1 retreatment after default and 3 retreatments after failure. Sputum microscopy was positive in 15 patients. Drug sensitivity tests showed 12 resistances only to isoniazid and rifampicin (HR), 2 extensively drug resistant TB (XDR-TB) and 9 resistances to HR and at least one additional drug. Most of them received treatment with Pyrazinamide, Ethambutol, Kanamycine, Protonamide, Ciprofloxacin and Cycloserine. Duration of treatment varied between 2 and 24 months. The treatment outcomes were: 8 had successful treatment, 5 were still continuing at the time of analysis, 4 failed, 3 died and 3 defaulted.

Conclusions: Treatment success rate in MDR-TB-HIV co-infected patients in Romania was 34.8% in the 4 analyzed years. Management of MDR-TB in sero-positive patients need to be improved.

P1935
Multidrug-resistant TB in children with HIV infection in Romania
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A retrospective study on a group of 417 children with TB and HIV/AIDS; 165 among these have had (+) culture for TB; MDR-TB - diagnosed to 73 children – 17.6%.

Results: Mean age – 14.5 years; Sex – M: 50.94%; F: 49%; TST positive – 5 mm – 51.5%; negative – 49.5%; associated clinical symptoms: fever, weight loss, irritability – 100%; pain throat 75%, haemoptysia 50%

Rx abnormalities: parenchymal infiltration – 36.4%; cavitary lesions – 37%, hilar opacities – 11.3%; miliary – 7.5% bronchopneumonic opacities – 7.5%.

Side effects of treatment: hepatic cytolytic syndrome – 35.1%; jaundice – 18.9%; hadeache – 16.2%; personality disorders – 16.2%; thrombocytopenia – 13.5%.

Bacteriological situation of discharge last BK examination BK cultures negative – 71.4%; positive – 28.6%.

Conclusions: The MDR-TB prevalence is increased in the HIV/AIDS infected children; more frequent in the children with multiple hospitals admittance with previosly antituberculosis therapy. History of inappropriate regimes drugs, preventive therapies, treatment interruptions, treatment with two drugs.

P1936 The risk of tuberculosis disease among HIV infected patients after 2 years of follow up Elena Daniels1, Ozana Cristina Anghier1, Claudia Cambrea2, Milea Mănăș1, Erdin Borgazi1, Sorin Rugina2.

Background: The risk of developing Tuberculosis (TB) disease is considered to be up to 7-10% each year for persons who are infected with both Mycobacterium tuberculosis (MTB) and HIV, whereas it is 10% over a lifetime for persons infected only with MTB. The aim of the study was to assess the risk of TB disease among HIV infected persons, based on different clues for tuberculosis' positive diagnosis, in a TB burden area, Constanta County.

Design: Prospective study started in 01 February 2009, ended in 31 January 2011. Material and methods: Evaluation for TB disease diagnosis was done in 51 HIV patients with initiated active antitubercular therapy (HAART) after 1996 and included medical history, physical examination, Mantoux Tuberculin skin test, chest X-rays, Blood blood culture results, bacteriological exam (Acid Fast Stains smear and Lowenstein Jensen cultures). All 51 HIV infected patients were monitored 2 years in order to diagnose the active TB diseases.

Results: The study includes 51 HIV infected people, 22 male and 29 female, mean age 20.5 years. The HIV infection range was within 6 months to 20 years. The risk of developing TB disease was of 21.5% (n=11/51). The prevalence of Pulmonary TB disease was greater (n=9/11;80%) than extrapulmonary forms. The symptoms of high fever, chronic cough, weight loss and diarrhoea were more persistent and more severe for HIV infected patients. Tuberculin skin testing and chest X-ray evaluation were helpful for diagnosis. Only one case had positive bacteriological exam.

Conclusions: The risk of developing active TB diseases at HIV infected people is much higher than studies reported. The bacteriologic exam is less helpful for TB diagnosis.

P1937 Primary drug resistance in HIV/TB patients Vera Zimina1, Irina Vasilyeva1, Aleksey Kravchenko2, Farid Batirov3, Irina Viktorova4, 1TB, Central Tuberculosis Research Institute, Moscow, Russian Federation; 2TB, Central Tuberculosis Research Institute, Moscow, Russian Federation; 3TBIVH, Tuberculosis Hospital #7, Moscow, Russian Federation; 4State Medical Institute for Postgraduate Training, Novokuznetsk, Russian Federation.

The aim of the study was to examine the frequency of MBT detection and the spectrum of primary drug resistance in HIV-positive patients with TB depending on the degree of immunosuppression. A study of 304 HIV-positive new TB cases registered during 2006-2010 with median CD4 count 140 cells/μl was carried out in Tuberculosis Hospital #7 (Moscow, Russian Federation). The mean age was 31.6±6.4 years.

Etologic confirmation of TB was obtained in 56.9% of patients (n=173), including those from sputum (35.2%; n=107), and the rest (n=66) from other materials (exudate, urine, cerebrospinal fluid, discharge from the fistula, biopsy material). Patients with CD4+ <100 cells/μl and with CD4+ ≥350 cells/μl were found to be smear and/or culture positive more frequently (42.7%, n=53 and 42.0%, n=18 respectively) than those with CD4+ 100-349 cells/μl (26.2%, n=36, p<0.05).

Drug susceptibility test was conducted in 126 patients on Lowenstein-Jensen media using absolute concentration method. MBT were susceptible in 48.4% of patients (n=61). 7.1% of isolates were monoresistant, polypersistence was found in 15.1% (n=19) (in most cases to combination of streptomycin or isoniazid – 57.9%). MDR TB was detected in 29.4% of patients (n=37) (including 4 cases of XDR, 3.2%). It should be noted that MDR was recorded in 35.4% of patients with CD4 + lymphocytes <200 cells/μl (28 out of 79), whereas the level of MDR in patients with CD4+ >200 cells/μl was 19.2% (9 out of 47) (p<0.005). Resistance to fluoroquinolones was registered in 7.1%.

Conclusion: Primary MDR was detected in every 3rd HIV/TB patient. The results of the study suggest the frequency of MBT detection from sputum in HIV/TB patients, as well as frequency of MDR, depends on the degree of immunosuppression.

P1938 The molecular-genetic methods in the express diagnostics of tuberculosis pleurisy (PTB) in HIV-infected patients Vasilekov Zharavelev1, Kirill Vladimirov2, Irina Vasilyeva1, 1Laboratory of Genetic Methods of Research, The Research Institute of Phthisiopulmonology, St. Petersburg, Russian Federation; 2Phthisiopulmonology, I.I. Mechnikov Medical Academy, St. Petersburg, Russian Federation.

84 HIV infected patients suffering with PTB admitted to TB hospitals. 42 had only PTB, 28 had suffered with pulmonary and PTB and 14 had multorgan TB. All the patients had new TB cases and no one of them obtained anti-retroviral therapy prior to admission. We studied pleural fluid in 84 and pleural biopsies in 16 cases. In all the patients pleural fluid was obtained during needle aspiration in a routine fashion. In 16 cases with PTB a thoracoscopic pleural biopsy was made to verify the diagnosis. Real time polymerase chain reaction (PCR-RT) and TB-biochip (TBCh) were performed. TBCh identifies mutations in four MBT genes associated with drug resistance (DR) to rifampin (R) rpoB and to isoniazid (H) katG, inhA, abpC. Sensitivity of PCR-RT was 55.9% (n=47) for pleural fluid and 75% (n=12) for the biopsies. Mutations in rpoB gene were found in 29 (61.7%) of cases, among them 22 (75.9%) due to replacement of the codon 531 (Ser-Leu). Other replaced codons were 511 (n=3), 516 (n=3), 526 (n=2) cases. We revealed DR to H, caused by mutations in katG gene in 25 (53.2%) cases, mostly in the codon 315 – 23 (92%). Mutations in other genes were rare: 4 (8.5%) in inhA and 1 (2.1%) in abpC. Mutations associated with DR to both H and R were present in 22 (44.7%). High prevalence of strains with combination of rpoB531 and katG315 mutations confirms the continuing presence of the pool of DR strains of Beijing genotype at the territory of North-West region of Russia in conditions of wide application of R in HIV infected patients. Our data suggest that PCR-RT and TBCh of pleural fluid and biopsies are highly sensitive for express detection of DR TB in the patients suffering with pleurisy and HIV.

P1939 Value of third sputum specimen for microscopic detection of pulmonary tuberculosis in HIV infected patients Majid Marjani, Payam Tabarsi, Parvaneh Baghaei, Mohammad Reza Masjedi, Ali Akbar Velayati. Clinical Tuberculosis and Epidemiology Research Center, National Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran.

Objectives: This study performed to evaluate sensitivity of two versus three sputum smears for diagnosis of pulmonary tuberculosis in patients with HIV co-infection. Methods: The study was done in National Research Institute of Tuberculosis and Lung Disease, Tehran, Iran. Data of patients with pulmonary tuberculosis and HIV co-infection was gathered from 2006 to 2009. New cases of tuberculosis that their disease diagnosed by positive sputum smear with acid fast staining and confirmed by positive culture in Lowenstein Media were selected. Results of first, second and third sputum were assessed. Results: Among 133 HIV infected patients with mean age of 40±9.5 and mean CD4 cell count of 82±12 cells/mm^3 sensitivity of first, second and third sputum smears for detection of acid fast bacilli was 83.5%, 84.1% and 82% respectively. First or second sputum specimens were positive among 95% of them. Extra diagnostic yield of the third sample was only 5%. Conclusion: In HIV infected patients who are suspected to pulmonary tuberculosis, two sputum specimens are enough for primary evaluation.

P1940 Adverse effects of treatment in HIV-associated tuberculosis patients in Iran Parvaneh Baghaei Shiva, Payam Tabarsi, Majid Marjani, Mohammad Reza Masjedi. Clinical Tuberculosis and Epidemiology Research Center, National Research of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran.

Background: We intend to assess the frequency of adverse effects of tuberculosis treatment in HIV patients.

Methods: The study was conducted at National Tuberculosis referral center in Iran, 2005-2010 including all documented TB patients with HIV co-infected. All patients received anti-TB treatment based on National TB Program. All adverse effects (AE) observed in patients were recorded in our registry.

Results: Of the total 151 TB/HIV patients, 81 (53.6%) developed adverse effects (AE), whether major or minor. Major AE (65) included: fever (46), convulsions (4), thrombocytopenia (17), rash (5) and 86.2% of them had CD4+ <100 (p<0.001). There were no differences between uses of HAART, outcome of treatment and major AE. Other AE did not show statistical significant in our study.

Conclusion: This study showed that major adverse effects do not affect to outcome of TB treatment.
Methods: We aimed to evaluate the results of TST (retesting if the first was negative) and two IGRA (T-SPOT.TB and QuantiFERON-TB GOLD In Tube) in 164 IBT patients from our hospital. Concordance between IGRA and TST was evaluated using kappa test.

Results: 164 patients were enrolled. TST was positive in 47 (28.7%) of 164 patients. The concordance between TST and T-SPOT.TB was low (kappa: 0.215, p < 0.001) (Table 1), the same as TST and QuantiFERON (Kappa 0.230, p < 0.001) (Table 2), and between T-SPOT.TB and QuantiFERON was moderate (Kappa 0.413, p<0.001).

Overall, 57 patients (34.8%) were diagnosed as LTBI (47 for positive TST and 10 more were detected by positive IGRA with TST negative result); the joint performance of two IGRA increased the percentage of patients diagnosed of LTBI (21.3% [95% CI, 8.5%-34.0%]); 8 out 10 positive-IGRA and negative-TST patients were receiving steroids therapy.

Conclusions: In IBD patients, concordance between TST and the two IGRA studied (T-SPOT.TB and QuantiFERON) was in general low. Performance of two IGRA altogether increases the number of IBD patients diagnosed of LTBI.
P1946
Tumor nekrosis factor-alfa blockers and tuberculosis – Analysis of the 6 years of Sergin Börekçi1, Berra Duman1, Nejdiye Mazican 1, Koray Tasçılar1,2, Beniam Miscellin1, Güll Öngör1, Vedat Hamuryudan1, 1Department of Pulmonary Disease, University of Istanbul, Cerrahpasa Medical School, Istanbul, Turkey; 2Division of Rheumatology, University of Istanbul, Cerrahpasa Medical School, Istanbul, Turkey.

Aim: It is a known fact that risk of tuberculosis infection is increased with tumor necrosis factor-alfa (TNF-α) blocker treatments. In this study we evaluated the last 6 years follow up data of the patients who admitted to our clinic for tuberculosis scanning before and during TNF-α blocker treatment.

Method: Total of 2335 patients’ follow up data were evaluated between February 2005 and February 2011. Statistical analysis were done by using SPSS 15.0 statistical program.

Results: There were 1186 (51%) male, 1149 (49%) female of total number of 2335 patients. Mean age was 40±14±6.7 years. Patients with the diagnosis of rheumatoid arthritis 785 (33.6%), ankylosing spondylitis 912 (39.1%), psoriatic arthritis 193 (8.3%), Behçet disease 85 (3.6%), Chroen disease 65 (2.8%), juvenile rheumatoid arthritis 142 (6.1%). 781 (33.9%) of the subjects had smoking history of an average 15.07±13.57 pack-year. 792 (33.9%) patients treated with Etanercept, 725 (31.0%) Infliximab, 567 (24.3%) Adalimumab. 66 (2.8%) patients had treatment for tuberculosis in the past, 112 (4.8%) patients had diabetes mellitus. According to RAED II (The Society for Research and Education in Rheumatology) Guideline; PPD was ≥ 5 mm in 1340 (57%), 101 (4.3%) had radiological fibrous lesion, 12 (0.5%) had contact history with tuberculosis. 1308 (56.0%) patients were given preventive treatment with Isoniazid. In these 6 years follow up, 4 (171/100.000) patients had tuberculosis infection; 2 were miliary tuberculosis (one of them was multidrug resistant), 1 was gastrointestinal tuberculosis and the last one was relaps patient with a history of tuberculosis.

Conclusion: This results supported that close follow up of patients who used TNF-α blocker was so important.

P1947
Quantiferon-TB GOLD vs. TST methods of detection tuberculosis infection in rheumatoid arthritis patients with previously TNF-z inhibitors treatment
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Introduction: TNFα inhibitors play an important role as therapeutic agents for certain chronic inflammatory diseases, but this treatment influences the subject’s immune status and can lead to opportunistic infections, including the TB.

Objective: Assessment of the sensitivity of the QuantiFERON-TB GOLD (QFT) method versus the tuberculin skin test (TST) in detecting TB infection on a group of patients with rheumatoid arthritis previously treated with Infliximab.

Methodology: Selection of a group of 52 rheumatoid arthritis patients treated before with TNFα inhibitors, diagnosed with pulmonary or extra pulmonary tuberculosis. On these 52 subjects TST and QFT were performed, observing the 6-monthly confirmed cases).

Results: From the processed data we observed that in the group of 23 patients with confirmed tuberculosis infection, 14 have had TST positive results (60.87%) and 10 were QuantiFERON-GOLD positive (45.4%).

Conclusions: QFT is an important method of TB infection diagnosis, but in patients undergoing chronic treatment with TNFα inhibitors it doesn’t show a greater sensitivity than TST.

P1948
Pulmonary tuberculosis (PT) in patients taking the TNF-a inhibitor infliximab (INF)
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Depression of TNF-a functions by its inhibitors not only suppresses the immune-inflammatory process, but also results in certain depression of an organism immune protection level and in increase in its susceptibility to TB. The medical and X-ray data of 263 patients taking INF for treatment of rheumatoid disease were analyzed. The features of PT in patients taking INF were studied. All the patients every 6 months undergo X-ray examination of the lungs. The PT has developed in 8 patients taking INF and was diagnosed in 4.6±2.5 months of therapy, the number of infusions was from 2 to 6. The PT was diagnosed after respiratory complaints, in 5 patients the MBB was isolated from the sputum. Studying of Mantoux test with 2 TE before the INF course has shown that this method does not provide any reliable information, because all the patients before that have been taking immunosuppressive hormonal therapy for a long time. The X-ray archive analysis has not resulted in identification of any pathological changes. In case of detection of the disease in 5 patients there were visible multiple changes in both lungs, it was mostly changes in the upper lobes of the lungs. 3 patients with focal dissimilation had infiltrates with small destruction cavities. All the patients had typical expressed bilateral enlargement of all groups of lymph nodes, tumor type with polycyclicity of the contours. The lymph nodes structure was normal. Rapid development of PT infection is typical for all the patients with tendency to generalisation and expressed hyperplasia of intrathoracic lymph nodes. In order to determine the risk of TB before administration of INF it is necessary to carry out quantiferon test and SCT.

243. Lung cancer: molecular pathology and functional genomics

P1949
Inhibition of hypoxia-induced phenotype alterations through epithelial-mesenchymal transition (EMT) in lung cancer by gene modulation of phosphorilation sites in tumor suppressor PTEN
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Recent studies suggested that hypoxia modulate epithelial-mesenchymal transition (EMT) process. For this measurement we evaluated the biological activities of PTEN, by which cell proliferation and migration are involved, could be regulated by phosphorilation in its e-terminal. In this study, we analyzed whether gene modulation of PTEN phosphorilation sites could inhibit hypoxia-induced phenotype alterations through EMT in lung cancer cells. GFP and GFP-PTENmut were transduced into lung cancer H358 with the doxycyclyne (Dox) inducible gene expression system. Dox-induced expression of GFP and GFP-PTENmut in H358 were confirmed by western blot analysis. Both the Dox-treated cells with GFP or GFP-PTENmut under hypoxic condition showed the decreasing expression of Epacrinin and the de novo expression of fibrocin in EMT and significantly increased the migration ability. Only the Dox-treated cells with GFP-PTENmut kept the expression E-cadherin and inhibited the de novo expression of fibrocin against hypoxia condition. Furthermore, these cells showed the significant repression of cell migration even under hypoxia condition, supported by the finding of suppressed expression of Akt and FAK phosphorylation. In this study, gene trasduction and Dox induction did not affect cell proliferation. These findings suggest that the gene modulation of phosphorilation sites in PTEN might give a new therapeutic strategy to regulate metastasis in lung cancer.

P1950
Loss of orphan G protein coupled receptor GPRC5A is associated with metastatic disease and poor survival in patients with adenoacarcinomas of the lung
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Introduction: Orphan G protein coupled receptor (GPRC) 5A from the group GPCRs (GPRC5A) has recently been suggested to be a tumor suppressor of lung cancers. First results from knockout mice and human RNA analyses implied an association with adenoacarcinomas and poor survival. The aim of the present study was to identify prevalence and clinical significance of GPRC5A protein expression in non-small cell lung cancers (NSCLC).

Materials and methods: GPRC5A protein expression was analyzed by immuno-histochemistry using a tissue microarray containing samples from more than 2,000 lung cancer patients with clinical follow-up data (Mean: 35.2±3.4 months).

Results: GPRC5A expression was absent in 298 (17.4%) of approximately 1,700 analyzable NSCLC (n=792 squamous cell carcinomas, n=471 adenocarcinomas, n=309 large cell carcinomas and n=96 other NSCLC). 41% of all analyzed NSCLC showed moderate to strong cytoplasmic and membranous GPRC5A stain. Staining intensities were inversely correlated with high tumor cell proliferation (p<0.0001) and grading (p<0.05). In adenocarcinomas, absence of GPRC5A was seen in just 20 cases (4.2%) but was strongly associated with metastatic disease and staging (both p<0.0001). Cumulative survival was significantly lower in patients with adenocarcinomas lacking GPRC5A (p<0.01).

Conclusions: Loss of GPRC5A is linked to high tumor cell proliferation in NSCLC. In adenocarcinomas of the lung, it is not very frequent but is strongly associated with metastatic disease and poor prognosis. Therefore, GPRC5A expression seems to be an important prognostic factor.
P1951

RARE2 methylation level in blood for lung cancer assessment

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Background: Cell-free DNA bearing the same epigenetic changes as the tumor tissue is found in blood and can be a useful tool for tumor patients indicating their usefulness as complementary diagnostic and prognostic markers for lung cancer.

Methods: Blood samples of 30 healthy men and 50 patients with confirmed non-small-cell lung cancer (NSCLC) before and after surgery were enrolled in this study. Methylation level of RARb2 gene in the cfDNA from blood plasma and cfDNA eluted from blood cell surface with PBS/EDTA and trypsin solutions was assessed by quantitative methylation-specific PCR.

Results: It was found that RARb2 gene methylation level was significantly increased in plasma cfDNA and cell-surface-bound cfDNA from NSCLC patients compared with healthy subjects (7620 copies/ml and 1083 copies/ml in the cell-surface-bound fraction, 3589 copies/ml and 1068 copies/ml in the blood plasma, Mann-Whitney U test, P<0.05). The increase of RARb2 methylation level was associated with stage and unfavorable outcome of the disease. 93% of NSCLC patients demonstrated the significant decrease of RARb2 methylation level in cfDNA at the time point of 10-15 days after surgery.

Conclusions: Epigenetic alterations of RARb2 gene in the total cfDNA were found to be associated with lung cancer progression. Correlation of RARb2 methylation level with tumor stage, outcome of disease and surgical treatment efficacy demonstrate applicability of cfDNA methylation marker assessment as a valuable tool for lung cancer prognosis and treatment monitoring improvement.

P1952

Quantitative methylation profiles of multiple genes in patients with non-small cell lung cancer and its association with clinicopathological correlations

Milica Konc1, Jelena Stojmc1, Dragana Jovanovic2, Vera Bunjevacki2, cell lung cancer and its association with clinicopathological correlations

Methods: Primary tumor samples (n=65), corresponding of non-malignant lung tissues (n=65) and blood samples (n=51) were obtained from NSCLC patients, treated with curative resectional surgery. Hypermethylation status was quantified at multiple CpG sites within each promoter in multiple genes—SOX1, RASSF1A, HOXA9, CDH3, MGMT, ESR1 and DAPK by pyrosequencing.

Results: For most of the genes there was a significant difference between tumor methylation, normal tissue and blood samples. Methylation in tumors was significantly higher than in normal lung for SOX1, DAPK, RASSF1A, HOXA9 and CDH3. Tumor hypermethylation was more frequently for adenosarcoma at CDH3 and ESR1. A higher proportion of SSC tumors were hypermethylated at HOXA9 and SOX1 compared to other types of NSCLC. Patients with stage four more likely had hypermethylation at MGMT and patients with hypermethylation at HOX9 more likely had stage two and three tumors. Gender was associated with hypermethylation at CDH3 with females being more likely to have hypermethylated tumors.

Conclusions: Our results show that elevated methylation levels observed in genes SOX1, RASSF1A, HOXA9, CDH3, MGMT, ESR1 and DAPK were cancer-specific and associated with some clinicopathologic features of patients.

P1953

The risk of distant metastases and prognosis prediction in early stage squamous cell lung cancer (SqCLC) by means of 3 microRNAs expression assessment

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Methods: The clinical significance of plasma DNA quantification in NSCLC and to explore whether these mutations are restricted to an adenocarcinoma component.

Aims: KRAS and EGFR oncoproteins have proven to be clinically significant as predictive or prognostic factors in non-small cell lung cancer (NSCLC). These genetic alterations are poorly investigated in squamous cell carcinoma (SCC). In the single study we evaluated the frequency of these cancer relevant mutations in adenocarcinoma (ADC) and SCC and therefore sought to gain further insights into the significance of EGFR in NSCLC and to explore whether these mutations are restricted to an adenocarcinoma component.

Materials and methods: Tumor samples of 741 patients suffering from stage III to IV NSCLC were investigated. KRAS mutations were examined by means of two independent analytical methods (Sequenom and SNaPshot). The molecular status of EGFR exon 19 and exon 21 were analyzed by fragment analysis. Mutations in EGFR exon 18 were assessed by direct sequencing.

Results: The 741 NSCLC samples comprised 149 (20.1%) SCC and 592 (79.9%) ADC. No coexisting mutations of EGFR and KRAS occurred in ADC and SCC, respectively. EGFR mutations were detected in 9 of 149 (6%) SCC (5.4% in exons 19 and 21).

Conclusions: KRAS and EGFR oncoproteins have proven to be clinically significant as predictive or prognostic factors in non-small cell lung cancer (NSCLC). These genetic alterations are poorly investigated in squamous cell carcinoma (SCC). In the single study we evaluated the frequency of these cancer relevant mutations in adenocarcinoma (ADC) and SCC and therefore sought to gain further insights into the significance of EGFR in NSCLC and to explore whether these mutations are restricted to an adenocarcinoma component.
Activating mutations of the EGFR gene are present in NSCLC and respond to EGFR TKI therapy, but 50% of these patients show disease progression during the course of TKI treatment, possibly due to resistant tumor cell clones primarily present as small clones within the carcinoma. We tested 80 adenocarcinomas of the lung for known EGFR mutations and using different methods for mutation analysis, and tried to correlate the new adenocarcinoma classification with EGFR mutational status. The study included 40 samples with proven mutation status and 40 patients with primary lung tumors. We applied several methods for mutation analysis, and compared to each other our results show a better specificity and better sensitivity. Cases analyzed by LightCycler assay and pyrosequencing showed 100% correspondence to 454 sequencing, whereas all other methods showed aberrations. Mutations present in small tumor cell clones were not detected by any of the other methods. Furthermore, T790M resistance mutation combined with an activating mutation could be found in 2 untreated patient samples. The results underline the need for higher sensitivity methods applicable in routine diagnostics.

Evaluation of highly sensitive PNA-LNA PCR clamp method for EGFR L858R mutation detection in lung adenocarcinoma patients

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Objective: Direct sequencing is widely accepted method for EGFR mutation identification, but has limited sensitivity. It often requires additional procedures, like microdissection, to enrich the sample in cancer cells, when their content in tissue specimen is less than 50%. PNA-LNA PCR clamping represents allele-specific approach to gene analysis and demonstrates potent accuracy and ability to detect mutant alleles even in present in low fraction of cells.

Method: 79 DNA samples isolated from fresh-frozen and FFPE tissues, which mutation status was formerly confirmed by sequencing, were analyzed by PNA-LNA PCR clamping for EGFR point mutation L858R in exon 21.

Results: L858R mutation was detected in 8/79 (10%) samples by direct sequencing, whereas in 12/79 (15%) samples by PNA-LNA PCR clamping. All mutant-positive samples by sequencing were correctly determined by PNA-LNA PCR clamp. The remaining 4 L858R mutant-positive samples were recognized as wild type by sequencing. Two of them contained only 5% and 20% of cancer cells, respectively. Surprisingly, in the other two samples PNA-LNA PCR clamping method detected only low levels of EGFR mutant allele, despite the cancer cell content were high (100% and 80%).

Conclusions: PNA-LNA PCR clamp technique enables sensitive and reliable detection of EGFR mutant allele in specimens with cancer cell content insufficient for direct sequencing or genetically heterogeneous. Regarding its extremely high sensitivity, PNA-LNA PCR clamping should be validated thoroughly prior implementation into EGFR diagnostic routine to prevent overdiagnosis.

Evaluation of four different molecular methods for EGFR mutation analysis in exons 18, 19 and 21

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Aims: EGFR mutation status detection is essential for comprehensive NSCLC treatment Most Non Small Cell Lung Carcinomas are analyzed by histological examination of a biopsy obtained by bronchoscopy. However, presence of very small amounts of tissue is available. These conditions require methods, suitable for the detection of very small amounts of mutated DNA. The aim of this study was to compare the sensitivity of mutation detection of four different molecular methods.

Methods: 237 cases with NSCLC were included. All biopsies were formalin fixed and paraffin embedded. DNA was isolated after microdissection of tumor tissue from 20 μm slides, exons 18, 19 and 21 of the EGFR gene were investigated using pyrosequencing (PS) and BioFilm Chip Hybridization (Chip). Additionally, a LightCycler assay was performed for Exon 19 (LC). All mutations were independently confirmed by Sanger sequencing.

Results: We determined 197 cases with mutations. 40 with mutations, 26 mutated in Exon 19. Chip: 24 samples, of which 4 mutated, could not be analyzed due to insufficient DNA amplification. Exon 19: 26 out of 26 detected correctly. PS: 39 of 40 mutations were detected. Exon19: 25 out of 26 detected correctly. LC (target only Exon 19): 25 of 26 were recognized correctly by this method.

Discussion: A comparison of methods showed no significant difference in sensitivity. Moreover, the Chipmethod failed to generate a sufficient PCR product out of very small amounts of DNA. Surprisingly, in the other two samples PNA-LNA PCR clamping method detected mutations positive.

Non-coding RNAs as functional player and molecular marker in lung cancer

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Objective: For direct sequencing or genetically heterogenous. Regarding its extremely high sensitivity, PNA-LNA PCR clamping should be validated thoroughly prior implementation into EGFR diagnostic routine to prevent overdiagnosis.

Materials and Methods: We tested with 1, Stefanie Grund1, Arne Warth2, Heike Zabeck3, Catherina Hildendrath1, Marion Baas1, Michael Meister1, Thomas Muley1, Peter Schirmacher1, Hans Hoffmann1, Philipp Schnabel2, Sven Diedrichs1, 1Helmholtz University-Junior Research Group Molecular RNA Biology & Cancer, German Cancer Research Center (DKFZ) & Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; 2Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; 3Department of Surgery, Thorasklinik Heidelberg, University Hospital Heidelberg, Heidelberg, Germany; 4Translational Research Unit, Thorasklinik Heidelberg, University Hospital Heidelberg, Heidelberg, Germany

Discussion: A comparison of methods showed no significant difference in sensitivity. Moreover, the Chipmethod failed to generate a sufficient PCR product out of very small amounts of DNA. Surprisingly, in the other two samples PNA-LNA PCR clamping method detected mutations positive.

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Objective: To assess the expression landscape of this new class of molecules, we have profiled the expression of 17000 non-coding RNAs in comparison to 22000 protein-coding mRNAs in early stages of lung adenocarcinoma and matched non-malignant lung tissue. These studies revealed molecular signatures associated with tumorigenesis (tumor vs. normal, diagnostic value), with histological subtypes (acinar vs. solid) as well as with the outcome and metastasis development (prognostic value).

Methods: Eight novel, differentially expressed transcripts named “Lung Cancer intergenic LNA” (LncRaI1 - LncRaI8) were validated and selected for functional characterization, for which we have implemented several technologies. To identify the molecular RNA-protein-networks in which the ncRNAs could function, we use RNA affinity purification and mass spectrometry. To study loss-of-function phenotypes in human lung cancer cells, we have developed a novel technique to create functional knockouts of ncRNAs in human lung cancer cell lines using Zinc Finger Nucleases. This strategy allows the specific and stable silencing of the targeted ncRNA without off-target effects for functional studies. Our research uncovers the functions at the cellular and molecular level of the differentially regulated ncRNAs as well as their clinical importance as diagnostic and prognostic markers.

Polymorphisms A1026G and G369C of CDKN1A/p21 and p53 genes in lung cancer

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In this study, we analyzed the polymorphisms of genes regulating the cell cycle and p53 CDKN1A/p21 as factors of genetic predisposition to lung cancer in patients with lung cancer. We examined 65 patients with lung cancer (average age 58.7 ± 12.3 years) and 100 healthy blood donors (average age 52.6 ± 12.7 years). Diagnosis of lung cancer was confirmed morphologically, endoscopically and radiologically. The study of these genes was performed by PCR/RFLP analysis. 72-GC- polymorphism analysis of p53 gene has revealed a slight increase in the frequency of the variant G72C-genotype of the p53 gene in lung cancer patients compared with those in healthy (38 and 32% respectively, P = 0.695).

We have also analyzed two polymorphisms CDKN1A/p21: 1026 A/G and 369 G/C; polymorphism in the 5′-gene promoter. In analyzing the 1026-A/G-p21 gene polymorphism was found halving the frequency of AG-genotype in lung cancer
patients compared with those in healthy individuals (38 and 77%, respectively; OR = 0.72, CI95% 0.81-3.95). The frequency of AA-genotype of p21 gene in patients and healthy was respectively 50 and 19% for the GG-genotype of p21 gene was respectively 40 and 6%; OR=0.53, CI95% 1.27-2.42). This enabled us to assume that the AG-genotype performs protective and AA-genotype - the role of predisposing to cancer of the lung. The frequency of A-allele in lung cancer patients was higher than in healthy individuals (70 and 57.5%, respectively). OR of lung cancer for carriers of the A-allele was 1.72 (CI95% 1.05-2.83).

In the analysis of G369C-gene polymorphism in p21 is shown, the frequency of C-allele in lung cancer patients significantly exceeded in that in healthy individuals (20.77 and 11%, respectively; OR=2.12, CI95% 1.10-4.09).

P1964

Expression profiling in hypoxic non-small cell lung cancer explants reveals a four-gene hypoxia signature

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Background: Hypoxia is frequent in solid cancers like lung cancer and contributes to chemotherapy resistance. To identify patients with hypoxic tumors would be of advantage. Direct oxygen measurements are of limited use, thus, feasible hypoxia markers are needed.

Material and Methods: A novel ex-vivo model was established using fragmented non-small cell lung cancer (NSCLC) specimens cultured three days under hypoxia (1% oxygen) or normoxia. cdNA microarrays were performed on hypoxia and normoxic fragments derived from ten patients (five adenocarcinomas, five squamous cell carcinomas). Correction for multiple testing was performed using FDR5.

Results: Histomorphology and viability/apoptosis tests confirmed the viability of the fragments. HIF-1α immunostaining and expression of carbonic anhydrase IX mRNA were increased in hypoxia. Microarray analysis revealed 129 regulated genes with at least two-fold expression change in hypoxia compared to normoxia. Hypoxia-induced gene expression was histology-dependent, only four genes were significantly regulated in both subtypes.

Conclusions: Our novel ex-vivo model is suitable to study hypoxic adaptation in lung cancer. Its advantage is the use of real tumor tissue maintained under different oxygen concentrations. cdNA expression profiling revealed a four-gene hypoxia signature that might be useful in therapies aiming to restore tumor perfusion and oxygenation.

P1965

Contribution of immunohistochemical (IHC) markers to the diagnosis of pulmonary carcinoids

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Introduction: Data about prevalence and clinicopathological meaning of IHC markers in pulmonary typical (TC, n=114) and atypical (AC, n=86) carcinoids is still debated. The goal of this study was to present expression patterns of several IHC markers in TC and AC. To get an insight on differential diagnostic, prognostic, and potential therapeutic value.

Methods: 200 pulmonary carcinoid tumors were investigated for tissue distribution of: CD56, CD57, Chromogranin A, Synaptophysin, TTF-1, CK18, KL1, ERC21, EGFNR, and Her-2/neu. Ka67 was employed and the proliferative index (PI) was counted on whole slides of resected specimens.

Results: Mean PI was 1.8% in TC and 3.7% in AC and was significantly different in both groups (p<0.0001).Correlation between PI and mean mitotic count was significant. Furthermore, max PI correlated significantly with outcome. Established neuroendocrine markers Synaptophysin, Chromogranin A, and N-CAM (CD56) were strongly positive. Synaptophysin was expressed with highest intensity of all markers in 95.4% TC and 98.6% AC. Thyroid transcription factor 1 (TTF-1) was positive in 73.0% TC and 77.0% AC. Only few cases expressed EGFR and Her2/neu.

Conclusions: Our model demonstrates that expression of Synaptophysin, Chromogranin A and N-CAM are sufficient for a fast and accurate diagnosis of TC and AC. Further studies are needed to establish other markers as potential diagnostic and prognostic tools.
Conclusions: Synaptophysin may be the most sensitive marker for neuroendocrine differentiation. Nevertheless, there is no specific marker to clearly separate TC from AC. We confirm that the PI, as determined by Ki67 staining is higher in AC than in TC and might be an ancillary tool for the distinction between TC and AC in addition to the mitotic rate. Moreover, the combination of PI and mitotic count in terms of a grading system may predict outcome more effectively than mitotic count alone and should be subject to further research.

P1966

Genetic polymorphism of alpha 1 antitrypsin and glutathione S transferase and lung cancer risk
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Background: Polymorphisms for genes encoding alpha 1 antitrypsin (A1AT) and glutathione S-transferase (GSTM1/GSTT1) might contribute to the variability in individual susceptibility to lung cancer.

Objectives: This is a cross-sectional, randomized, case control study for the evaluation of the frequency of A1AT (M, Z and MZ) and GST (GSTM1/GSTT1 null) alleles among patients with lung cancer. The study included 56 cases of lung cancer diagnosed patients (histopathological examination), recruited from the Pneumology Hospital Leon Daniello Cluj and 125 healthy unrelated controls, selected among patients observed in the Internal Medicine Department.

Methods: A1AT genotyping was carried out using PCR amplification of relevant gene segment was followed by restriction enzyme digestion TaqI. Detection of A1AT gene S and Z alleles was determined through analysis of resulting restriction fragment length polymorphism (RFLP). For GSTM and GSTT genotyping we used multiplex PCR, followed by gel electrophoresis analysis.

Results: The molecular analysis identified the MS genotype in 3 (5.4%) patients with lung cancer and 1 (0.8%) of the controls. The heterogeneous MZ state was detected neither among cases nor in controls. The prevalence of GSTM null genotype in lung cancer patients was 49.4% compared to 42.8% of controls, also the prevalence of GSTT null genotype in lung cancer patients was 24.5% compared to 18.2% of controls.

Conclusions: Our findings (positive statistical significance) suggest that heritable A1AT and GST status may influence the risk of lung cancer development.

P1967

Quality matters in lung cancer diagnosis: Comparison of endobronchial cryobiopsy with conventional forceps biopsy
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Introduction: Endoscopic forceps biopsies are often small and inadequate for detailed analysis whereas biopsies obtained with cryoprobes may provide tissue samples that are larger and better preserved. We compared the quality and complication rate of endoscopic forceps- and cryobiopsies.

Methods: Prospectively collected data of patients who underwent cryobiopsy (CB, n=14) were compared with randomly selected patients who had conventional forceps biopsies (FB) during the same period (n=13). All patients were considered prospectively to have definite endobronchial tumour. Sample size and quality was assessed. Complication rate and final diagnosis were also recorded.

Results: Maximum sample diameter was significantly larger in the CB group (median 1.6cm, range 0.7-3.0cm) compared to the FB group (median 0.5cm, range 0.3-1.3cm, p<0.001). All biopsy samples were diagnostic of malignancy apart from 1 CB sample showing necrosis only. Semi-quantitative analysis showed a smaller proportional tumour area within the biopsy when forceps were used (median 50%, range 0-90%) compared to the cryoprobe technique (median 90%, range 50-100%, p<0.001). 6 of 13 FBs had artifact changes affecting up to 90% of the biopsy whereas only 1 CB had minor artifact changes of 5%. 1 FB patient had mild bleeding. Mild and moderate bleeding were seen in 2 CB patients, respectively.

Conclusions: Cryo biopsy appears to provide larger and higher-quality tumour specimens than conventional forceps biopsy. These differences may become important in an era of targeted therapies for individual patients, when multiple testing of biopsies is required. We believe the technique of cryobiopsy merits further evaluation.

P1968

Bronchoscopic cryoablation gains high diagnostic rate in submucosal tumor growth
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Introduction: The diagnostic yield of endoscopic biopsy in the central bronchial system is impaired when submucosal tumor growth is present. Conventional forceps biopsy fails to reveal conclusive histology even in cases of extrabronchial compression or other indirect tumor signs. Since endoscopic cryotechniques have increasing impact for diagnoses of malignant and inflammatory lung disease we compared the diagnostic rate of forceps and cryoprobe in patients with suspected submucosal tumor growth.

Methods: 116 patients with macroscopic submucosal tumor infiltration were investigated prospectively with forceps- and cryobiopsy from 05/2009 to 02/2011. In cases 1-3 forceps and 1-2 cryoprobe specimens were obtained, other biopsy methods were added as needed. Specimens underwent routine histopathological processing.

Results: Histological diagnosis was achieved with the following specimens: Forceps 4/116 pts. (3.5%), cryo 48 (41.4%), forceps/cryo 34 (29.3%), cryo/TBNA 2 (1.7%), cryo/EBUS 6 (5.2%), forceps/cryo/EBUS 2 (1.7%), forceps/cryo/EBUS 2 (1.7%), TBNA 4 (3.5%), EBUS 12 (10.3%). CT-guided biopsy 2 (1.7%). Hit the target point in 18 (21.6%) cases. The diagnostic rate in the central bronchial submucosal tumor growth we found a relevant difference of diagnostic yield and a decisive superiority of cryotechnique, which should be considered for routine use in diagnostic bronchoscopy.

P1969

Does routine use of EBUS-TBNA and EUS-FNA improve the accuracy of staging of non small cell lung cancer patients – A national tumor registry based study
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Background: Evaluation of the extend of disease or stage (TNM) is a prerequisite for correct treatment of lung cancer. Several studies have showed that biopsies and fine needle aspirations obtained by EBUS-TBNA and EUS-FNA yield similar results as mediapso, which previosly have been considered the standard for evaluation of mediastial nodal involvement in NSCLC. Thus EBUS-TBNA and EUS-FNA should now be considered as procedures which are equally effective as mediastinoscopy in staging while at the same time being more gentle to the patient.

Material: We therefore used data from a population based lung cancer registry to evaluate the association between frequency of use of EBUS-TBNA/EUS-FNA and precision of mediastinal work-up. EUS in diagnostics and staging of lung cancer have been used in several centres for more than a decade and since 2005 several centres have inter grated EUS in their procedures.

Results: The material consisted of 7000 operated patients since 2003. The use of endoscopic ultrasound (EBUS-TBNA/EUS-FNA) was mostly used in one region and mediastinoscopy in another. The concordance between n and p were highest and equal in the regions where mainly mediastinoscopy were used and the reason where Endoscopic Ultrasound was used

Conclusion: For the first time it is possible to get an impression of the impact of the use of EBUS-TBNA and EUS-FNA in a national populationof lung cancer patients. The we no difference in the pT/pN ratio in the areas where they used mediastinoscopy and where they used endoscopic Ultrasound.

P1970

Impact of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) in the evaluation of mediastinal adenopathy in lung cancer
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Introduction: TBNA is an established technique for sampling mediastinal nodes in the diagnosis and staging of lung cancer. The advent of EBUS-TBNA has allowed the respiratory physician to access more and sample smaller nodes than mediastinoscopy in staging while at the same time being more gentle to the patient.

Aims: To determine the diagnostic yield, sensitivity and specificity of conventional TBNA (CTBNA) and EBUS-TBNA in our unit.

Methods: Data collected included patient characteristics, nodes sampled, pathological diagnosis and clinical outcome. Following EBUS introduction, this data was collected prospectively over a 6 month period.

Results: 63 TBNA procedures were performed in the months preceding EBUS introduction. The overall diagnostic yield was 71.43% (n=45) and 46.67% (n=21)

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of these specimens were from station seven. 78 specimens were acquired via EBUS-TBNA in the first 6 months of the programme. The diagnostic yield was 83.3% (n=65), 42.3% (n=32) samples were from station 7, 28.1% (n=22) from 4R, 5.1% (n=4) from 4L and 9% (n=7) from 10R. Sensitivity for cancer improved from 80.65% in the CTBNA group to 83.3% in the EBUS-TBNA group despite a dip to 75% in the first 3 months of the programme when analysed separately. Specificity was 100%. There were no major complications.

**Conclusions:** EBUS-TBNA was associated with improvement in diagnostic yield and sensitivity for lung cancer nodal involvement when compared to conventional techniques. A clear learning curve was seen but overcome within 3 months. This improvement in yield and the ability to sample more nodal locations may reduce referral for surgical or repeat procedures.

**P1971** Evaluation of endobronchial ultrasound-guided needle aspiration selected samples – The point of view of pathology
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Some studies were done to compare EBUS-TBNA with other methods. The diagnostic finding of the EBUS-TBNA probes and every other medical report of the patient was recorded. Malignancies were subdivided in NSCLC NO, Ade- nocarcinoma, Squamous Cell Carcinoma, Small Cell Carcinoma other than the lung cancer and Malignancies NO. The same localisation of the lung analysed with TBNA was examined with another method such as resection or biopsy in selected cases. With this data, the accordance between the sampling techniques was controlled. Of these 222 TBNA probes, from lymphode station 7, 10, 4 and 2 such as upper thoracal lesions, in 206 (93%) cases a diagnose (tumor or-not-tumor) was made, in 16 (7%) cases no clear diagnosis could be made concerning the worse tissue quality.

Sensitivity for cancer improved from 80.65% in the cTBNA group to 83.33% in the the EBUS-TBNA group despite a dip to 75% in the first 3 months of the programme when analysed separately. Specificity was 100%. There were no major complications.

**Conclusions:** EBUS-TBNA was associated with improvement in diagnostic yield and sensitivity for lung cancer nodal involvement when compared to conventional techniques. A clear learning curve was seen but overcome within 3 months. This improvement in yield and the ability to sample more nodal locations may reduce referral for surgical or repeat procedures.

**P1973** Can mediastinoscopy after negative endosonography in lung cancer be omitted? Subanalysis of ASTER with focus on PET
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**Background:** Mediastinal staging in non-small cell lung cancer with endosonography (EUS-FNA plus EBUS-TBNA) followed by mediastinoscopy is more sensitive to detect nodal metastasis as compared to mediastinoscopy alone (ASTER trial, JAMA 2010;304:2245). However 11 patients need to undergo a mediastinoscopy to detect one with N2/3 missed by endosonography. We analysed if FDG-PET identifies patients in whom the mediastinoscopy can be omitted.

**Methods:** In ASTER, 123 patients were randomized to endosonography followed by mediastinoscopy when the former did not show mediastinal metastasis. Sensitivity, negative predictive value (NPV) and number of mediastinoscopic needed to detect one false negative endosonography were calculated in the cases with complete data (n=120, 98%).

**Results:** With PET, 77 patients had FDG-avid mediastinal nodes; the prevalence of N2/3 was 73 (62-81%). The sensitivity and NPV of endosonography was 88 (76-94) and 75 (57-88%). Adding mediastinoscopy increased sensitivity and NPV to 96 (88-99) and 91 (73-98%). 43 patients did not have FDG-avid mediastinal nodes, the prevalence of N2/3 was 23 (13-38%). The sensitivity and NPV of endosonography was 70 (40-89%) and 92 (78-97%). Adding mediastinoscopy increased sensitivity and NPV to 80 (69-94%) and 94 (81-98%). In patients with FDG-avid vs. FDG-cold mediastinal nodes, the number of mediastinoscopic needed to detect one false negative endosonography is 6 vs 36 (p=0.078).

**Conclusions:** A negative endosonography should be followed by a mediastinoscopy if PET positive mediastinal nodes are present. In the absence of PET positive nodes, a mediastinoscopy following a negative endosonography can be omitted.

**P1974** Risk of lung cancer in patients with preinvasive bronchial lesions followed by autologous bronchoscopy and chest computed tomographyP1974
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**Introduction and aim of the work:** To assess risk of lung cancer (LC) in patients with preinvasive bronchial lesions and to identify factors associated with higher risk.

**Patients and methods:** 124 patients with one or more preinvasive bronchial lesions and normal chest computed tomography (CT) (mean age 66.7 years, 121 males and 3 females), followed-up by white light and autofluorescence bronchoscopy (AFB) every 4-6 mo and chest CT every 6-12 mo, end points were development of carcinoma in situ (CIS) or LC.

**Results:** Among 124 patients with 240 preinvasive bronchial lesions, 20 CIS or LC lesions were detected during follow-up in 20 (16%) patients, 7 were detected as new endobronchial lesions, 10 as new peripheral lesions and 3 as local progression from severe dysplasia to CIS. Median time to progression was 24 months (range: 6-54 mo). The Cumulative risk of progression was 7% at one year, 20% at three years and 44% at 5 years. Among detected lung cancers, 80% were stage 0 or stage I and underwent treatment with curative intent. Diagnosis of new SD during follow-up (p=0.001), chronic obstructive pulmonary disease (COPD) (p = 0.001) or smoking index >52 pack-year (p = 0.042) was associated with higher risk. Even after controlling for other risk factors, COPD was associated with risk of progression. Baseline lesion grade was not predictive of patient outcome (p = 0.146).

**Conclusions:** Patients with preinvasive bronchial lesions, especially those with new SD during follow-up, COPD or smoking >52 pack-year are at high risk of LC, AFB and CT follow-up facilitated early detection and treatment with curative intent.

**P1975** Validation of diagnostic molecular markers in bronchial fluid for lung cancer
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**Aim:** To set a diagnosis method in bronchial fluid to detect lung cancer (LC) with high sensitivity. For this, using proteomic techniques, we have identified some biomarkers which are increased in patients with LC.

**Material/Methods:** We have included bronchial aspirates samples from 204 patients diagnosed with lung cancer by biopsy 141 non-microcytic (NSCLC) (59
adenocarcinoma and 82 epidermoid), 63 microcytic (SCLC) and 49 control patients with other non malignant pathologies.

Immunohistoassays have been performed based on ≈MAP technology (lumines X) for each specific molecular marker. Once the assay has been designed and optimized, the amount of each marker has been quantified in each sample. Both groups were controlled with control group using t-student test. The diagnostic capacity of each marker has been evaluated by ROC curve. Finally, model was obtained by multivariate logistic regression analysis.

Results: Immunohistoassays have been performed by IHC, for each marker, such as NCC, as SCLC cancer, in bronchial aspirates samples: - 5 markers that detect NSCLC with sensitivity of 95% and specificity of 77% have been observed. The calculated ROC area was 0.95. - 6 markers that detect NSCLC with sensitivity of 95% and specificity of 81% have been observed. The calculated ROC area was 0.96.

Conclusions: Some protein markers are expressed differently in patients with cancer, not only NSCLC but also SCLC, and in patients without cancer. These proteins detect these tumors with high sensitivity and specificity. Due to this, these markers could be used to design a diagnostic test in clinical routine.

P1976
 Curette lavage fluid analysis of EGFR, KRAS, and P53 mutations in lung cancer patients
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Purpose: Mutation analyses of individual lung cancer patients should provide useful information for determining treatment. When sufficient tissue samples for pathology cannot be collected by bronchoscopy, cytology is substituted to establish diagnostic resection. The present study evaluated liquid cytological material (LCM), from brush biopsies (EBs), for detecting the EGFR, KRAS, and P53 mutations in tissues attached to the curette were analyzed by collecting the lavage fluid.

Subjects: Samples were obtained from 63 lung cancer patients receiving treatment from April, 2009 to October 2010 at the Department of Respiratory Medicine, Showa University Fujigaoka Hospital. Official approval for the study was obtained in advance by the Ethics Committee for Genomic Research at Showa University.

Methods: DNAs were extracted from cells in the curette lavage fluid. PCRs were performed using amplification mutation hot spot regions in EGFR, KRAS, and P53. The PCR products were sequenced and the mutations confirmed by sequencing with the ABI 3730 capillary.

Results and discussion: Seven patients were found with EGFR mutations and seven with P53 mutations. No mutation in KRAS was identified. The mutation rates observed here for the three genes were lower than those reported previously with both forward and reverse primers.

Conclusion: EGFR mutation gene analysis.

P1977
 Clinical utility of EGFR gene mutation analysis with cytological materials from bronchoscopy not histological materials
 Kyosuke Nakata, Yoshikazu Kotani, Yukihisa Hatakeyama, Nanako Tomita, Nobuko Hazeki, Akihito Sashika, Kazuyuki Kobayashi, Yasuhiko Funada, Yoshihiro Nishimura. Division of Respiratory Medicine, Kobe University Hospital, Kobe, Hyogo, Japan

Rationale: Epidermal growth factor receptor (EGFR) gene mutation analysis becomes essential in medical cares for non-small-cell lung cancer after the report of the effectiveness of Gefitinib for non-small-cell lung cancer patients who have EGFR gene mutations. Although most of materials for EGFR gene mutation analysis in the past reports or clinical practice is submitted from lung tissue, we recently identified. The mutation rates observed here for the three genes were lower than those reported previously with both forward and reverse primers.

Conclusion: EGFR mutation gene analysis.

P1978
 Prognostic impact of angiogenesis factors in bronchoscopic washing fluid from patients with non-small cell lung cancer
 Andriani Chapadola1, Christina Fevragoulou1, Marinos Zontanos1, Ioannis Danos2, Panos Demetrizis2, Ioannis Gozios1, Kostas Syrigos1. 1Oncoology Unit, 3rd Dept of Medicine, Athens School of Medicine, 7th Pulmonary Dept., 3rd Pulmonary Dept., Sotira General & Chest Hospital, Athens, Greece

Background: Angiogenesis has been proven to be a process related to the migration, proliferation and metastasis of cancer cells. The prognostic value of angiogenesis factors is controversial.

Aim: The aim of this study is to define the VEGF, VEGFR1 and VEGFR2 and the ratios of VEGF/VEGFR1 and VEGF/VEGFR2 in the blood serum and the washing of patients with newly diagnosed non-small cell lung cancer (NSCLC).

Methods: 40 patients with NSCLC participated in this study. The measurement of circulating (c) and washing (w) levels of VEGF, VEGFR1 and VEGFR2 was carried out with the ELISA method.

Results: cVEGF levels is correlated with T descriptors in TNM staging system (r=0.021), as well as the ratio VEGF/VEGFR2 in serum and washing (r=0.03 and r=0.040 relatively). From those who were treated with chemotherapy, best responses were observed in lower concentrations of VEGF in serum and washing (r<0.001). Higher concentrations of wVEGF are correlated with worse overall survival (HR 2.28, 95%CI 1.13-4.19, P=0.002) and PFS (HR 2.66, 95%CI 1.45-4.48, P=0.019). Similar results for OS and PFS were observed with high values of the wVEGF/VEGFR2 ratio. Multivariate Cox analysis revealed as independent markers for overall survival VEGF, VEGFR1 and VEGFR2 in serum and washing (r=0.017 and r=0.034 relatively), while for PFS independent markers were VEGFR1 (r=0.04), VEGF/VEGFR1 (r=0.03) and VEGF/VEGFR2 (r=0.007) in washing.

Conclusions: The circulating levels of VEGF and VEGFR2 are controversial. Nevertheless, the difference in detection sensitivity of washing might allow to recognize a risk group of patients who could benefit from an agressive initial therapeutic approach.

MONDAY, SEPTEMBER 26TH 2011

P1979
 Does immediate cytological analysis at bronchoscopy lead to reduced number of biopsies?
 Chakwada Eunchi, Maria Manalo, Behdad Shambayati, Paul Murray. Respiratory Medicine, Ashford and St Peter’s Foundation Trust, Surry, United Kingdom

Introduction: The British Thoracic Society guidelines [1] for diagnostic flexible bronchoscopy in adults are currently under review. Present guidelines highlight the importance of needing five endobronchial biopsies (EBs) to optimise diagnostic yield. The aim of our study was to find out whether the availability of a cytopathologist during bronchoscopy has led both to a reduction in the number and need of EBs performed.

Method: The study period was March to October 2010. We reviewed whether the use of immediate analysis of brush biopsies or tumour roll on EBs performed had led to a reduction in the number of EBs performed by comparing the number of biopsies performed during this period to numbers performed prior to our in-room cytopathologist set up. We also reviewed 14 consecutive patients who had EBs performed during the study period to look at both how many biopsies tended to be first pass positive and how many biopsies in total were taken per patient.

Results: We found that the availability of a cytopathologist within the bronchoscopy room has led to a significant reduction in the number of EBs performed without detriment to diagnostic rate or further testing like IHC and EGFR status. Of the 14 patients who had EBs 85% of cases were first pass positive with the mean of total biopsies taken being two.

Conclusion: Our retrospective study shows that the availability of an in-room cytopathologist reduces the number of biopsies performed, and thus associated complications. Furthermore our small cohort demonstrates that even without a cytopathologist the recommended five EBs is unnecessary.


P1980
 The efficacy of cytology sampling in the diagnosis of suspected endobronchial lung cancer
 Farhana Shora, Gulam Haji, Haider Ali, Frances Bowen. Clinical Infection & Respiratory Medicine Directorate, Imperial College Healthcare NHS Trust, London, United Kingdom

Introduction: Fibreoptic bronchoscopy (FOB) is a minimally invasive procedure that is regularly performed on an outpatient basis to aid diagnosis in suspected endobronchial lung cancer, not only NSCLC but also SCLC, and in patients without cancer. These investigations are normally performed by the cytopathologist set up. We also reviewed 14 consecutive patients who had EBs performed during the study period to look at both how many biopsies tended to be first pass positive and how many biopsies in total were taken per patient.

Method: The study period was March to October 2010. We reviewed whether the use of immediate analysis of brush biopsies or tumour roll on EBs performed had led to a reduction in the number of EBs performed by comparing the number of biopsies performed during this period to numbers performed prior to our in-room cytopathologist set up. We also reviewed 14 consecutive patients who had EBs performed during the study period to look at both how many biopsies tended to be first pass positive and how many biopsies in total were taken per patient.

Results: We found that the availability of a cytopathologist within the bronchoscopy room has led to a significant reduction in the number of EBs performed without detriment to diagnostic rate or further testing like IHC and EGFR status. Of the 14 patients who had EBs 85% of cases were first pass positive with the mean of total biopsies taken being two.

Conclusion: Our retrospective study shows that the availability of an in-room cytopathologist reduces the number of biopsies performed, and thus associated complications. Furthermore our small cohort demonstrates that even without a cytopathologist the recommended five EBs is unnecessary.

positive histology alone. 3 (20%) cases had positive cytology but negative histology in the context of an endobronchial lesion. All 7 patients without an endobronchial lesion had negative cytology and were subsequently found not to have cancer. Only 1 patient with an endobronchial lesion had both negative histology and cytology and was proven not to have cancer.

Conclusion: From this retrospective analysis we conclude that 20% of lung cancers would have been missed if cytological samples had been taken in addition to endobronchial biopsies. Therefore we suggest that any patient with an endobronchial lesion should have brushings and washings accompanying a biopsy. We cannot deduce from our small study whether, in the absence of a visible endobronchial lesion, brushings and washings are diagnostically valuable.

P1981
Relative contribution of cytological specimen type in the determination of lung cancer histologic identity – Analysis of one year’s comparative data
Stylianos Michaelides1, Aphrodite Emmanouilidou2, Georgia Goulas1, Ageliki Lazaratou1, Despina Melemeni1, Aikaterini Blana2, Vassilios Handrininos1, 11st Dept. of Thoracic Medicine, 2Dept. of Clinical Cytology, Simmangon General Hospital, Maroussi, Athens, Attiki, Greece

We retrospectively evaluated the relative contribution of cytological specimens in identifying the histologic type of lung cancer. Seventy-four patients (50 male & 24 female) aged 63.8±9.9 years (mean±SD), eventually diagnosed to have lung cancer were studied. Diagnosis was established by either bronchoscopic or surgical biopsy: The spectrum of cytological specimens included: simple sputum smear (SP), bronchial washings (BW), post-broncoscopic brushing (PB), brushing smears (BS) and transbronchial fine needle aspirates (FNAs). The distribution of histologic types was as follows: Small Cell Lung Cancer (SCLC) 24 pts (32.4%), Squamous Cell Carcinoma 20 pts. (27%), Adenocarcinoma 14 pts. (18.9%), Undifferentiated Carcinoma 6pts. (8.3%), Large cell Carcinoma 2 pts. (2.8%). Analysis of data showed that simple sputum cytology was diagnostic in 24.3% (relative contribution 66.6% [confidence interval 53-34% for NSCLC]). Success rate of BW was 42% (although equally partitioned between SCLC & NSCLC 52% & 48% respectively). BS di- agnosed 23% of lung cancer, of which 56.3% was the yield for adenocarcinoma. The contribution of FNA smears cannot be evaluated due to the very small sample size (only 2 patients which was successful in both).The overall contribution of cytology in the diagnosis among all types of lung cancer cases studied was 57 pts among a total of 74 (77%). We conclude that simple sputum cytology should not be neglected (having a diagnostic rate of 25% of patients) while the significance of BS in adenocarcinoma (56.3%) should be emphasized given its frequent peripheral location that does not allow obtaining tissue for histologic diagnosis.

P1982
Liquid-based cytology in the diagnosis of pulmonary malignancy in bronchial brushings and washings
Beata Olejnicka1, Annika Dejmek1, Agneta Westman2, Nooredin Zennedeh2
1Department of Medicine, Trelleborg Hospital, Trelleborg, Sweden; 2Department of Clinical Pathology and Cytology, University Hospital, Malmo, Sweden

Background and aims: Bronchial cytology (BC) is well established in the diagnosis of lung cancer but some cases remain equivocal. Liquid-based cytology (LBC) was developed to improve the diagnostic accuracy and increase the sensitivity for malignancy in BC. The study was conducted to compare the diagnostic performance of CytoRichRed (CRR) fixed TriPath preparations with conventional smears (CS) from bronchial brushings (BB) and bronchial washings (BW).

Methods: BB and BW from 61 patients, subjected to fiberoptic bronchoscopy were studied. BB specimens were split into two equal parts, one part was fixed in CRR and prepared according to the TriPath protocol, one part was ethanol-fixed and stained according to Papanicolaou. BBs were smeared onto slides, air-dried and Giemsa-stained, then brushes were rinsed in CRR and the cellular suspensions were processed according to the TriPath technique. Slides were evaluated in a blinded fashion and cytological diagnoses were compared with “true” diagnoses, based on histology and clinical data.

Results: In all 575 and 244 CS and 61 and 61 CRR/Tripath slides were prepared from the BB and the BW, respectively. CS diagnoses agreed in 57/61 cases. In the four discrepant cases the conventional/CRR diagnoses were atypia/benign, benign/atypia (malignancy favoured), benign/equivocal, atypia (active favoured/benign. All four cases turned out to be malignant.

Conclusions: The diagnostic accuracy did not differ between conventional and CRR/Tripath preparations. Our results indicate that LBC using CCR/Tripath can replace CS, significantly reducing work load and cost.

P1983
Endobronchial ultrasound and fluoroscopy in the study of peripheral lung lesions
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Endobronchial ultrasound (EBUS) is a minimally invasive tech-

nique that expands the view of the bronchoscopist beyond the lumen of the airway. Radial probe EBUS (eREBUS) is used for the detection of peripheral lung lesions. Aim: To analyze the diagnostic yield of eREBUS in peripheral pulmonary lesions. Methods: All patients who underwent bronchoscopy to study peripheral lung lesions from January 2009 to February 2011 were prospectively included. Patients were randomly distributed in two groups: fluoroscopy and REBUS (30 patients, 20.4±7.8 years) or fluoroscopy alone (64 patients, 68.1±10.9 years). All procedures were performed under fluoroscopic guidance with iv conscious sedation. eREBUS was performed using an endoscopic ultrasound system (EU-M60, Olympus, Tokyo, Japan), equipped with a 20 MHz mechanical radial type miniature probe (UM-BB S20-17S). Bronchoscopist, cytologist, study protocol, techniques and tools were the same ones throughout the whole study.

Results: 94 patients (68.4±10.6 years) with peripheral pulmonary lesions suspicious of malignancy were studied. The average size of these lesions was 35.2±13.3 mm in eREBUS group vs 41.8±19.6 mm in fluoroscopy group (n.s). In 26 cases (27.6%) the size was <30 mm: 7 cases (23%) in eREBUS group vs 19 (29%) in fluoroscopy group (n.s). Global diagnostic yield was 73% using EBUS whereas it was 67% when using fluoroscopy alone (n.s.). Diagnostic yield in lesions <30 mm was higher in eREBUS (86% vs 58%, n.s.). No complications were reported related to REBUS or iv sedation.

Conclusions: eREBUS is a promising, useful and safe technique for the diagnosis of peripheral pulmonary lesions, especially in those of small size.

P1984
Diagnosis of pulmonary nodules localized beyond the range of standard bronchoscopere – 2011 results
Szymon Skoczynski, Grzegorz Brozek, Wladyslaw Pierzchala. Department of Pulmonology SP CSK in Katowice, Medical University of Silesia, Katowice, Poland

Background: There is a wide range of tools used in diagnosis of pulmonary nodules localized beyond the range of standard bronchoscopere, but it is still difficult to choose best method to obtain tissue samples.

Aims and objectives: The aim of our study was to assess safety and utility of methods currently used in Department of Pulmonology in Katowice, Poland, and to compare the obtained results to prepare diagnostic protocol to be tested in prospective study.

Methods: 93 consecutive patients records (56 females and 37 males) were analyzed. Included patients had at least one pulmonary nodule exceeding 10 mm in diameter, which on the basis of CT scan was not assessable by standard bronchoscopere. 

Results: 64 transbronchial biopsies were performed: 40 CT-guided cytolocal [22 (55%) diagnostic], 20 ultrasound guided cytolocal [10 (50%) diagnostic] and 4 ultrasound guided histological [all diagnostic] respectively. Pleural fluid was examined 8 times but only one pleurocentesis was diagnostic. Sputum analysis was performed 16 times but all results were not diagnostic. Out of 39 cases in which bronchofiberoscopy was performed 6 (15.9%) were diagnostic. All, except one positive diagnoses were pulmonary cancer. Out of 40 CT guided biopsies 17 (42.5%) were complicated by pneumothorax. In 3 (7.5%) cases drainage was required. Out of 20 ultrasound guided cytolocal biopsies there was 1 pneumothorax not requiring drainage. There were no observed complications in histological biopsies. The diameter of nodules in patients with positive diagnosis was bigger (p<0.05).

Conclusions: Accurate selection of diagnostic tools seems to be crucial for both an effective and safe diagnosis of pulmonary nodules.

245. Mechanical ventilation and lung injury: new advances

P1985
Late-breaking abstract: High flow oxygen therapy decreases endotracheal intubation requirement in patients with ARDS
Guillaume Schnelli1, 2, Claire Andrejak1, Bouchra Lamia1, Bédécourt Toublanc1, Jean-François Muir2, Antoine Cuvelier3, Vincent Jouanneau3, 1Pulmonary and Respiratory Intensive Care Unit, Amiens Teaching Hospital, Amiens, France; 2Pulmonary and Respiratory Intensive Care Unit, Rouen University Hospital & UPRES EA 3830, University of Rouen, Rouen, France

High flow oxygen (HFO) therapy is able to deliver up to 60L/min of a heated and humidified air-oxygen mixture through nasal cannulae and to provide small amount of positive end-expiratory pressure. Our objective was to assess the outcome of patients admitted for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) who were treated by HFO and to determine if HFO could decrease endotracheal intubation rate. We retrospectively selected 38 consecutive patients (median age 57 years) admitted to ICU for ALI (n=5, 13%) or ARDS (n=33, 87%) and who underwent HFO (Optiflow®, Fisher & Paykel, France) at admission (PaO2 < 65 mmHg, PaO2/FIO2 345s

345s

Farmacautice SpA, Visit Chiesi Farmaceutici SpA, at Stand D.30
Mauo-Ying Bien1,2,3, Yu Ru Kuo4, You Shui Lin6, You-Lan Yang1,\nventilation for weaning ICU patients from mechanical ventilation\nComparisons of predictive performance of breathing pattern variabilities\nP1987\nIn vitro performance of an improved collapsible holding chamber (CHC) for the\ndelivery of bronchodilators to patients receiving mechanical ventilation\nMark Nagel, Valentina Avvaokouma, Rubina Ali, Cathy Doyle, Jolyon Mitchell.\nMedical Aerosol Laboratory, Trudell Medical International, London, ON, Canada\nBronchodilator delivery by pressurized metered-dose inhaler (pMDI) to patients on mechanical ventilation is best achieved without breaking the breathing circuit. We describe an evaluation of an improved CHC (AeroVent Plus*, Trudell Medical International, London, Canada (n=5 devices, 1 measurement/device), in which the pMDI canister receptacle is offset from the CHC axis to reduce internal impaction, and can also accept GSK pMDI canisters having a dose counter. Delivery of 3-actuations of salbutamol (HFA Ventolin*, GSK Canada; 100 µg/actuation) was assessed with the expanded CHC inserted in the inspiratory limb of an adult breathing circuit equipped with a 7-mm diameter endotracheal tube (ETT). An adult test lung (Michigan Instruments) was used to simulate the patient. The circuit was humidified near to body conditions (T = 36°C, 100%RH), and tidal breathing (600-mL, duty cycle = 33%, 10 breaths/min) was simulated by a servo ventilator (Siemens, model 900C). A filter was located between the distal end of the ETT and tidal test lung to collect the aerosol. Total mass (TM) of salbutamol after 6 respiratory cycles was determined by HPLC-UV spectrophotometry. Similar measurements were obtained with a Spiral* CHC (Armstrong Medical), providing benchmark data from a European marketed CHC having the pMDI receptacle in-line with the axis of the device. TM (mean± SD) from the AeroVent Plus and Spiral CHCs was 22.7±3.1 and 47.0±7.1 µg/actuation respectively. Clinicians using these devices should be aware of the implications of the difference in drug output between these apparently similar devices.

P1988\nHigh-frequency oscillatory ventilation – A safe procedure for COPD patients?\nSven Pulizze1, Ute Achzetzh1, Andreas Pechtmann2, Ernst Schmid3,\nMichael Quint0,1, Norbert Weilger1, Inez French1, Department of\nAnaesthesiology and Intensive Care Medicine, University Medical Center Schennew.-Holstein. Campus Kiel, Kiel, Germany; 2 Department of Internal\nMedicine IV, Medical Center, Chemnitz, Germany; 3 Department of\Anaesthesiology, Emergency and Intensive Care Medicine, University Medical Center Göttingen, Göttingen, Germany\nIntroduction: High-frequency oscillatory ventilation (HFOV) is an alternative type of mechanical ventilation. HIFOV is usually considered as not indicated in patients with obstructive lung disease because of the theoretical risk of air trapping and hyperinflation.\nAim and objectives: Intention of this study was to establish if HFOV can safely be applied in patients with exacerbation of chronic obstructive pulmonary disease and hypercapnic respiratory failure.\nMethods: Ten patients with acutely exacerbated chronic obstructive pulmonary disease (GOLD stages II-IV) requiring intensive care treatment who failed on non-invasive ventilation were studied. After a period of mechanical ventilation (CMV) of less than 72 hours all patients were transferred to HFOV for 24 hours and then back to CMV.\nMain results: Regional lung aeration and ventilation were assessed by electrical impedance tomography. HFOV was tolerated well, no adverse effects were ob- served. Effective CO2 elimination and oxygenation were achieved. Arterial partial pressure of CO2 was 52±13 mmHg (mean ± SD) during CMV before transition to HFOV and 47±9 mmHg by the end of the 24-hour period of HFOV. Ventilation was more homogeneously distributed during HFOV than during initial CMV. No signs of hyperinflation induced by HFOV were identified. Higher respiratory rate and tidal volume were found during CMV after 24 hours of HFOV than before.\nConclusions: Contrary to present recommendations on the use of HFOV in adult patients our pilot study indicates that this type of mechanical ventilation can safely be used in patients with chronic obstructive lung disease.

P1999\nEfficacy of a ventilator bundle for the prevention of the ventilator-associated pneumonia\nFelipe Chertcoff1, Miguel Blasco1, Carolina Giuffre2, Lorenza Maldonado3,\nSergio Verbanaz2, Elias Solosa1, Emiliano Descotte1, Ernesto Efron2.\n1Respiratory and Critical Care Medicine, British Hospital, Buenos Aires, Argentina; 2Infectology, British Hospital, Buenos Aires, Argentina\nIntroduction: Several specific and general strategies have proven effectiveness for prevention of ventilator-associated pneumonia (VAP).\nObjective: To evaluate the impact of ventilator bundle and the control of process measures on the rate of VAP in our Intensive Care Unit.\nMethods: A prospectively ventilator bundle have applied to every patient who received mechanical ventilation (MV). Daily control of the application of ventilator bundle was registered and weekly control of ventilator bundle compliance was registered. We compare the VAP rate of two periods, 25 months before the implementation of the bundle and 11 months after. The Poisson regression test was used. The methodology of the NHSN (National Healthcare Safety Network) was used for infection surveillance and the methodology of IHI (Institute of Healthcare Improvement) was used for compliance control.\nResults: The MV use rate was higher in ventilator-dependent patients (1381/2253 = 0.61 vs. 2840/5262 = 0.54 p<0.0001), the MV average days was also higher during the bundle period (8.52±2.07 vs. 7.03±1.61 p<0.0001). The VAP rate was lower during the bundle period compare with the previous one (3.62% MV days vs. 12.32% MV days p=0.001) with a reduction of the VAP of 70.6%. The compliance to the ventilator bundle was 97.91% and the fulfillment of the ventilator bundle was 90.13%.\nConclusion: The application of a ventilator bundle and control of ventilator bundle compliance was associated with a diminishment of the VAP rate.

P1990\nEffects of N-acetylcysteine in lipopolysaccharide-induced acute lung injury in the rat: Treatment after acute lung injury\nJae Sung Choi, Ho Sung Lee, Ki Hym Seo, Ju Ock Na, Yong Hoon Kim.\nDivision of Pulmonary and Critical Care Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea\nIntroduction: As it has been known that N-acetylcysteine (NAC) which is a free radical scavenger and antioxidant reduces acute lung injury of rats stimulated by lipopolysaccharide, studies on NAC are being executed recently as a way of treatments of lung injuries. This study was to elucidate effect of NAC in LPS-induced acute lung injury in rats.\nMethods: Six weeks old SD rats were divided into 4 groups (group 1: saline; 2: NAC, group 3: LPS; group 4: LPS+NAC. LPS was intravenously injected at the rate of 5mg/kg. NAC of 20mg/kg was injected into abdominal cavity 3, 6 and 12 hours after the injection of LPS. BAL fluids and lung tissues were obtained from individual rats. Using 100mg of lung tissues, the levels of NF-κB and lipid peroxidation (LPO) were measured.

346s
Results: Neutrophilic inflammations of the lung tissues and BAL fluids were the most severe in the LPS group. The amounts of NF-kB in the group 3 (0.32±0.23 ng/μg) showed statistically significant differences compared with the group 1 (0.16±0.12 ng/μg) (p < 0.001) and 4 (0.25±0.19 ng/μg) (p < 0.05). The amounts of LPO in the group 3 (15.29±3.76 mmol/ml) showed statistically significant differences compared with the group 1 (4.35±4.27 mmol/ml), 2 (4.99±5.68 mmol/ml) (p < 0.01) and 4 (7.65±4.24 mmol/ml) (p < 0.05).

Conclusion: N-Acetylcysteine has a protective effect to reduce acute lung injury stimulated by endotoxin and it is considered that the mechanism appears in relation to neutrophils that are mainly involved in lung injuries.

P1991
C-reactive protein as a predictor of mortality in patients with severe sepsis in intensive care unit
Zulbul Karakuş, Ozlem Yazıcıoğlu Mocin, Orkan Devran, Nalan Adagüzel, Goksan Gungor, Merih Kalamuğan Balci, Ece Oz, Adnan Yılmaz. Intensive Care Unit, Suryayapapa Chest Diseases and Thoracic Surgery Training Hospital, İstanbul, Turkey

Objective: We aimed to research whether initial and/or third day of C- reactive protein (CRP) values can be good predictors of mortality as other well known complex predictors of mortality (ie, SOFA scores) for patients with severe sepsis requiring ICU.

Methods: Observational cohort study was done in a 20 beds respiratory ICU in chest diseases center in Istanbul in January 2009-March 2010. Patients with severe sepsis due to respiratory diseases (pneumonia, acute exacerbation of chronic obstructive pulmonary diseases, bronchectasis) were enrolled in this study. Patients with rheumatic diseases and cancer were excluded from study. SOFA scores and CRP values on admission, third day and mortality rate were recorded. The receiver operator characteristic (ROC) method and area under curve (AUC) were used to compare SOFA scores, CRP values.

Results: In study period 814 patients were admitted to ICU and eligible 314 patients (male 175, female 139) were included. Sepsis due to nosocomial infection, on 3rd day CRP values on admission, third day and mortality rate were recorded. The receiver operator characteristic (ROC) method and area under curve (AUC) were used to compare SOFA scores, CRP values.

Conclusion: Third day CRP values especially >100mg/L are better mortality predictor than first day CRP and as valuable as SOFA scores in patients with severe sepsis in ICU.

P1992
Mechanical properties of ALI/ARDS lung may be heterogenous
Massimo Crescioni1, Daniela Febres 1, Chiara Chiurazzi 1, Gallazzi Elisabetta 1, Eleonora Carlesso1, Davide Chiumello2, Luciano Gattinoni 1,2.

Objective: Mechanical properties of the recruited lung units was between the surrogate compliance of well inflated double the compliance of the poorly inflated tissue. As shown the median compliance of the well inflated tissue was almost triple range. As shown the median compliance of the poorly inflated tissue was almost double the compliance of the poorly inflated tissue while the surrogate compliance of the recruited lung units was between the surrogate compliance of well inflated and poorly inflated tissue.

Table 1. Specific lung tissue compliances

<table>
<thead>
<tr>
<th>Surrogate compliance</th>
<th>5-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not inflamed (g/t &lt; 0.1)</td>
<td>0.00 [0.00 to 0.00]</td>
</tr>
<tr>
<td>Recruit 5-15</td>
<td>0.040 [0.02 to 0.10]</td>
</tr>
<tr>
<td>Poorly inflamed (g/t &lt; 1)</td>
<td>0.033 [0.00 to 0.08]</td>
</tr>
<tr>
<td>Well inflamed (g/t &lt; 0.1)</td>
<td>0.061 [0.00 to 0.15]</td>
</tr>
<tr>
<td>Over inflamed (g/t &gt; 9)</td>
<td>0.132 [0.11 to 0.18]</td>
</tr>
</tbody>
</table>

Conclusions: As recruited regions while increasing PEEP reach a lower gas tissue ratio and a smaller compliance than well inflated tissue changes in compliance may not be used to estimate lung recruitment at bedside.

P1993
Lactate and lactate clearance were associated with higher mortality in patients with septic shock
Prapun Kittivoravitchai, Anan Wattanatham, Adisorn Wongsa. Pulmonary and Critical Care Division, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand

Introduction: An elevated lactate level is associated with higher mortality in patients with severe sepsis. Also, lactate clearance is a surrogate for magnitude and duration of global tissue hypoxia. However, the utility of the lactate clearance after ICU admission as an indicator of outcome in patients with septic shock is still limited.

Objectives: The purpose of study is to evaluate the advantage of lactate level and clearance in predicting mortality of patients with septic shock.

Methods: We prospectively enrolled 38 patients with septic shock in ICU at Phramongkutklao hospital. Measurements of venous lactate and ScvO2 were obtained at 0, 2, 6, 24, and 72 hours after ICU admission. Lactate clearance was defined as the percent change in lactate levels after 2 or 6 hours from the baseline value. The primary outcome was 28-day mortality rate.

Results: The 28-day mortality rate was 55.3%. There was no significant difference in 28-day mortality rate between normal ScvO2 (>70%) group and low ScvO2 (<70%) group at initial presentation. Using cut off value of 3 mmol/L, higher initial lactate level was significantly associated with higher 28 -d mortality (p = 0.017). There was also, significant association between lactate non-clearance (lactate clearance < 10%) at 2 and 6 hrs and higher 28-day mortality (p = 0.029 and 0.014).

Conclusions: Early lactate clearance may indicate a resolution of global tissue hypoxia and is associated with mortality. Patients with higher lactate clearance after 2 and 6 hrs of ICU admission have improved outcome compared with those with lower lactate clearance. Also, initial lactate level was independently associated with 28-day mortality rate.

246. Genetic and molecular background in pulmonary fibrosis

P1994
Mutations in SFTPC, SFTPA2 and TERT explain 60% of familial pulmonary fibrosis and correlate to specific disease phenotypes
Coline van Moorle1,2, Joanne van der Vis1, Matthijs van Oosterhout1, Henk Ruiven1, Pin de Jong1, Wouter van Es1, Jules van den Bosch1,2, Van Gruuters1,2. 1Centre for Interstitial Lung Disease, St Antonius Hospital, Nieuwegein, Netherlands; 2Heart & Lung Disease, University Utrecht, Utrecht, Netherlands

Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease, histologically characterized by diffuse interstitial remodeling and patchy inflammation. A significant number of patients with IPF have a familial form of the disease. Separate reports have identified mutations in Surfactant Protein C (SFTPC), Surfactant Protein A2 (SFTPA2), Telomerase Reverse Transcriptase (TERT) or Telomerase RNA component (TERC) in these families. We determined the frequency of mutations in SFTPC, SFTPA2, TERT and TERC in 20 patients with Familial Pulmonary Fibrosis (FPF).

Heterozygous non-tolerated sequence changes were detected in 12 out of 20 patients, consisting of 5 SFTPC, 2 SFTPA2 and 5 TERT mutations. Mutations segregated with disease in each family and haplotype analysis showed that identical mutations had arisen independently. Families with SFTPC and SFTPA2 mutations always had evidence of parent-offspring disease transmission, while in families with TERT mutation sibs were affected. Pediatric pulmonary disease occurred only in families with SFTPC mutations. Carriers of an SFTPA2 mutation also suffered from lung cancer. Families with a TERT mutation usually presented as typical IPF and did not show clear symptoms associated with other known syndromes of telomere shortening.

This is the first report of a cohort of IPF families that is completely sequenced for candidate genes. We could identify a mutation in 60% of patients with FPF. These mutations correlated with a specific disease phenotype. The function of each of the mutated genes is very different, but all indicate towards a central role for the alveolar type II cell in disease pathogenesis.
P1995
Association between polymorphisms in the P53 and P21 genes and IPF
Nicoline Korthagen1, Coline van Moorsel 1, Karin Kazemier 2, Jan Grutters 1,2.
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a devastating and progressive lung disease. Its aetiology remains unclear but is thought to involve damage to the epithelium and abnormal repair. Alveolar epithelial cells near areas of remodelling show an increased expression of proapoptotic molecules. The purpose of this study was to investigate the role of genes involved in cell cycle control in IPF.

Materials and methods: We included 353 controls and 77 IPF patients and determined genotypes for five polymorphisms in the P53 gene and four polymorphisms in CDKN1A, the gene encoding p21. In PBMC from 16 healthy controls mRNA expression of p53 and p21 was determined.

Results: The rs12951053 and rs12002273 polymorphisms in the p53 gene were significantly associated with survival in IPF patients. Carriers of the minor allele had a 4-year survival of only 22% versus 57% in the non-carrier group (p=0.006). All four polymorphisms in CDKN1A were significantly predisposed to IPF. The association between the polymorphisms and survival was with increased risk of developing IPF. In addition, the rs2395655 allele was associated with a rapid decline in lung function. The rs733590 polymorphism was significantly associated with p21 mRNA expression levels.

Conclusion: This study reports the novel finding that polymorphisms in the p53 gene are associated with survival and polymorphisms in the p21 gene predispose to IPF. This suggests cell cycle defects are involved in the pathology of IPF. Variations in the p53 and p21 genes may impair the response to cell damage and increase the loss of alveolar epithelial cells.


P1996
Genetic variability in the IL1RN gene and the balance between IL1-Ra and IL-1β in IPF
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a rapidly progressive interstitial lung disease of unknown etiology. Interleukin (IL)-1β plays an important role in inflammation and has been associated with fibrotic remodelling. We investigated the balance between IL-1β and interleukin-1 receptor antagonist (IL-1Ra) in bronchoalveolar lavage fluid (BALF) and serum as well as the influence of genetic variability in the IL1B and IL1RN gene on disease susceptibility and cytokine levels.

Materials and methods: In 77 IPF patients and 349 healthy controls, single nucleotide polymorphisms (SNPs) in the IL1B and IL1RN gene were determined. Serum and BALF IL-1Ra and IL-1β levels were measured using a multiplex suspension bead array system and were correlated with genotypes.

Results: BalF and a significantly increased IL-1Ra/IL-1β ratio was found in IPF patients compared to healthy controls. In the IL1RN gene, one SNP was associated with both the susceptibility to IPF and reduced IL-1Ra/IL-1β ratio in BALF.

Conclusion: Our results show that genetic variability in the IL1RN gene plays a role in the pathogenesis of IPF and that this role may be more important than until recently thought. IPF patients appear to have a disproportionate shortage of IL-1Ra, which might contribute to a pro-inflammatory and pro-fibrotic environment in their lungs.

P1997
The relationship of IL-4 cytokine gene polymorphisms, HRCT and histopathological score in patients with idiopathic pulmonary fibrosis
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a serious disease with unknown etiology, where an influence of cytokine gene polymorphisms is presumed. We compared HRCT alveolar (AS) and interstitial score (IS) and histopathological score with IL-4, and IL-4RA gene polymorphisms in IPF patients.

Subjects and methods: IPF was diagnosed in 46 patients according to ATS/ERS consensus criteria. 43 patients had evaluable HRCT investigations, 14 patients had surgical lung biopsy. HRCT scans were evaluated using IS and AS scales by Gay et al. The histopathological evaluation of lung biopsies comprised: myofibroblast foci (MF), inflammation, eosinophils, granulomas and Ashcroft criteria for fibrosis grading. The IL-4 (-1082) A/G (-590) AA/AG (-33) and IL-4 RA +1902 G alleles were characterized utilizing a PCR-SSP method.

Results: AS was higher in IL-4 haplotypes 1 TTC and TTTC carriers (p=0.0423). Ashcroft score was more advanced in IL-4 haplotype 2 GCC (p=0.013) and MF counts were higher in TCC carriers (p=0.0376). IL-4 RA +1902 A G and IL-4 RA +1902 A A T correlated with higher AS (p=0.035, p=0.0123). Ashcroft score was higher in IL-4 -1082 A G and IL-4 -33 A T carriers (p=0.0443, p=0.0915).

Conclusions: We assume that IL-4 and IL-4RA polymorphisms might influence the HRCT and histopathological phenotype of IPF. The correlation of all four relevant IL-4 genes polymorphisms (especially IL-4 -33 T) with AS could mean, that new alveolar lesions with continuing fibroses are more pronounced in these polymorphisms carriers. The positive correlation of IL-4 -33 A T with Ashcroft score might support a hypothesis of fibrogenic role of IL-4 in IPF.

P1998
Familial idiopathic pulmonary fibrosis and “genetic anticipation”
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Background: Telomere dysfunction can be associated to “genetic anticipation”, earlier age of onset and more rapid progression of disease in succeeding generations, well known in Dyskeratosis Congenita, due to heterogeneous TERC/TERC mutations (essential components of telomerase), which have been reported in 8-15% of families with Idiopathic Pulmonary Fibrosis (IPF) and 1-3% of non familial IPF.

Aims and objectives: Retrospective study to assess whether a form of genetic anticipation can be found in families with IPF and to establish clinical features and outcome of familial IPF in comparison to non familial IPF.

Methods: We reviewed all files of patients with familial IPF seen at our department (17 families consisting of a total of 37 individuals) and compared age at diagnosis, clinical progression, frequency of acute exacerbations and survival outcomes with a database of 162 patients with non familial IPF. We are sequencing TERT and TERC genes in patients with familial IPF.

Results: Among the familial IPF patients, 5 had their father or mother affected; in all these cases the son/daughter was diagnosed earlier than the parents (mean age 56.4 years vs 72.4) and had a more rapid progression (all patients had at least one disease progression during follow-up); mean age of diagnosis of siblings and non familial IPF patients was 60.9 years and 65.4 years respectively.

Conclusions: We hypothesize a type of genetic anticipation in families with IPF with the latest generations being most severely affected. We are sequencing TERT and TERC genes in these patients to demonstrate that genetic anticipation in Familial IPF is associated to the inheritance of shorter-than-normal telomeres in association with the defective telomerase activity.

P1999
Association of single nucleotide polymorphisms in 4 genes (VDR, COL1A1, CALC and BGLAP) with susceptibility to steroid osteoporosis in patients with idiopathic pulmonary fibrosis (IPF)
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Steroideal osteoporosis is a serious medical and economic problem. At the same time, osteoporosis is a polygenic disorder.

Aim: To assess effectiveness of steroid osteoporosis prevention by antiresorptive agents (ARA - Bisphosphonates, Calcitonin) in patients with IPF with different genetic predisposition to osteoporosis.

Subjects: 114 patients with IPF, 19 males, 95 females, age 56.7±10.6 years, treated with Corticosteroids (CS).

Methods: Bone mineral density (BMD) measuring by DEXA, patients’ questionnaires and genotyping were used. Genomic DNA was isolated from peripheral leukocytes. We investigated 5 SNPs by PCR-RFLP analysis in 4 genes: vitamin D receptor, collagen typel alpha1, calcium receptor and osteocalcin.

Results: Severity of BMD loss and bone fractures occurrence strongly correlated with CS cumulative dose (p=0.010 and p=0.001, respectively). Multiple regression analysis showed significant influence of only VDR-FokI on BMD (p=0.009), and BGLAP was about significant (p=0.081). Environmental factors, firstly ARA intake, seems to have stronger influence on BMD than genes (adjusted R 2=0.065).

Conclusion: ARA administration is necessary for all patients with IPF, irrespec-
tively of genotype. VDR-FokI analysis is useful to reveal subjects with increased risk of osteoporosis. In IPF it is necessary to implement BMD loss prevention. Further efforts are required to clarify weight of BGLAP.
P2000
The genetic polymorphism of metalloproteinases MMP2, 7, 9 and MMP inhibitor TIMP2 in sarcoidosis
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Background: Increased activity of metalloproteinases may play a role in the initiation and propagation of inflammation in sarcoidosis. It may also be one of the factors responsible for the development of lung fibrosis. The aim was to verify whether polymorphisms of MMP2.C735T, MMP7 A181G, MMP9 T1702A and tissue inhibitor of metalloproteinase (TIMP2)P2418C predispose to sarcoidosis.

Material and methods: 139 patients with sarcoidosis and 100 healthy subjects were included. MMPIs and TIMP2 mRNA were measured in peripheral blood lymphocytes using real time RT-PCR. DNA for genetic polymorphism was extracted from peripheral blood by GTC method. Protein concentrations in peripheral blood lymphocytes were measured by ELISA, and MMP2 and 9 activities in BAL fluid were estimated by gel zymography.

Results: TT genotype of MMP9 T1702A was more frequent in sarcoidosis (p=0.0001; OR=13.71, 95%CI 7.02-26.80) and resulted in higher expression of MMP9 mRNA (p<0.0001). There was no relation to radiological stages, lung function test parameters, activity markers and the presence/absence of Löfgren syndrome. There were no differences in the distribution of MMP2, MMP7 and TIMP2 polymorphisms. MMP2, 7, 9 and TIMP2 mRNAS, as well as concentrations of these molecules were elevated (p<0.0001 for each). Gel zymography did not show differences in MMP2 and MMP9 activity in BAL fluid between different genotypes.

Conclusions: The TT homozygote of MMP9 T1702A genotype may be predisposed to sarcoidosis. Elevated mRNAs of all these molecules suggest their inducibility.

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P2001
Dose-dependent pro- or anti-proliferative effects of calciuminhibitors in bronchiolar and allogeneic stem cell transplantation
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Background: Chorioblastin obliterators (BO) is a common complication after allogeneic stem cell transplantation (SCT), characterized by fibroproliferation, fibrotic occlusion of small airways, and poor prognosis. As BO is strongly associated with chronic graft-versus-host disease (GVHD), it is believed to be a pulmonary manifestation of chronic GVHD. The management of BO comprises the augmentation of immunosuppressive therapy, but treatment response is generally poor. Here, we showed that quercetin suppresses transforming growth factor-β (TGF-β) induced collagen production in NH3T3 cells and in normal human lung fibroblasts. This suppressive effect of quercetin was mediated by quercetin-induced HO-1. The suppression of collagen production was confirmed by the reaction product of HO-1, CO, but not by bilirubin. Furthermore, the translocation of the nuclear factor E2-related factor-2 (Nrf2), an important transcription factor that regulates the expression of HO-1 from the cytoplasm to the nucleus, was demonstrated in NH3T3 cells by exposure to quercetin. Assessment of the signal transduction pathway involved in TGF-β signaling showed that quercetin stimulated the Smad and mitogen-activated protein kinase pathway to varying degrees. Our results demonstrate that quercetin exerts suppressive effects on the expression of collagen by the induction of HO-1. Idiopathic pulmonary fibrosis is the most lethal diffuse fibroing lung disease, and is characterized by the deposition of extracellular matrix. Quercetin or its derivatives, which effectively induced HO-1, will lead to new therapeutic strategies for promoting antibiotic therapy in respiratory diseases.

Methods: We aimed at analyzing membrane-bound FasL expression on alveolar macrophages (AM) and lymphocytes (AL) as well as soluble FasL (sFasL) levels in bronchoalveolar lavage (BAL) from ILDs patients: pulmonary sarcoidosis (PS), hypersensitivity pneumonitis (HP), silicosis, asbestosis, idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), and healthy subjects (n=89,12,7,8,23,6,17, resp.).

Results: In IPF significantly increased percentage of AM FasL+ and CD8+FasL+ cells as well as sFasL in BAL were found. Increased sFasL levels were also observed in HP. NSIP and asbestosis were characterized by higher AM FasL+ receptor number; CD9+FasL+ proportion was expanded in asbestosis only. There was significant decline in AL FasL+ percentage in PS and HP. Systemic steroid treatment, assessed in PS and IPF subgroups, did not affect FasL expression. Smokers with ILD tended to present lower sFasL levels, but not BAL cell FasL+ numbers. Vital capacity was negatively correlated with sFasL, levels, AM FasL+, and CD8+FasL+ cell relative count. CD4+FasL+ and CD8+FasL+ percentage strongly correlated with BAL neutrophilia, an unfavourable prognostic factor of lung fibrosis.

Conclusions: The concurrent comparative BAL analysis for FasL expression indicates that FasL+ AM and AL (especially Tc cells) comprise an important element of the fibroproliferative process, mostly in IPF. FasL might play a crucial role in other fibrosis-complicated ILDs, like NSIP and asbestosis.

P2003
Heme oxygenase–1 induced by quercetin attenuates TGF-β-stimulated collagen production in fibroblasts
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Quercetin is a flavonoid with a wide variety of cytoprotective and modulatory functions. Heme oxygenase-1 (HO-1) is an inducible enzyme. Its reaction product, carbon monoxide (CO), confers cellular protection in a number of conditions and diseases associated with oxidative or inflammatory lung injury. Furthermore, quercetin was reported to be a potent inducer of HO-1 in several cell types. We hypothesized that quercetin suppresses the production of collagen in fibroblasts via the induction of HO-1. Here, we showed that quercetin suppresses transforming growth factor-β (TGF-β) induced collagen production in NH3T3 cells and in normal human lung fibroblasts. This suppressive effect of quercetin was mediated by quercetin-induced HO-1. The suppression of collagen production was confirmed by the reaction product of HO-1, CO, but not by bilirubin. Furthermore, the translocation of the nuclear factor E2-related factor-2 (Nrf2), an important transcription factor that regulates the expression of HO-1 from the cytoplasm to the nucleus, was demonstrated in NH3T3 cells by exposure to quercetin. Assessment of the signal transduction pathway involved in TGF-β signaling showed that quercetin stimulated the Smad and mitogen-activated protein kinase pathway to varying degrees. Our results demonstrate that quercetin exerts suppressive effects on the expression of collagen by the induction of HO-1. Idiopathic pulmonary fibrosis is the most lethal diffuse fibroing lung disease, and is characterized by the deposition of extracellular matrix. Quercetin or its derivatives, which effectively induced HO-1, will lead to new therapeutic strategies for promoting antibiotic therapy in respiratory diseases.

P2004
Different expression pattern of endothelin receptors in primary human lung fibroblasts derived from idiopathic pulmonary fibrosis compared to healthy controls
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Background: Endothelin-1 (ET-1) has a considerable fibrogenic activity and it has been implicated in the pathogenesis of pulmonary fibrosis. Increased levels of ET-1 have been demonstrated in serum and bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF), and lung tissue of IPF patients show increased ET-1 immunoreactivity. The biological effects of ET-1 are mediated through two receptors – ET-A and ET-B. However, disease specific patterns of ET receptor expression in fibrotic and normal primary human lung fibroblasts had not been reported yet.

Methods: Primary human lung fibroblasts were isolated and propagated from lung parenchyma derived from patients with IPF (n=8) as well as from parenchyma derived from healthy controls (n=8). Isolated cP狒 were grown to confluence.

Results: Transforming growth factor beta (TGF-beta) stimulation total protein was harvested and immuno blot analysis was performed.

Conclusion: Our data demonstrate for the first time a difference in the pattern of
Molecular mechanisms and pathogenesis of idiopathic pulmonary fibrosis (IPF) remain unclear yet TGF-β-induced differentiation and proliferation of fibroblasts/myofibroblasts are recognized as primary events.

We investigated the role of PI3K/Akt pathway in TGF-β1-induced proliferation of human lung fibroblasts and their differentiation into myofibroblasts. Moreover, we evaluated the expression of all PI3K class I p100 isoforms (α, β, γ and δ). By using selective inhibitors, we also dissected the functional role of these isoforms. Ex-vivo human lung fibroblasts were stimulated with TGF-β1 in the presence or absence of PI3Ks pan-inhibitor LY294002 as well as of selective inhibitors. Cell proliferation was evaluated by cell counts and WST-1 proliferation assay. Western blot analysis and the Sircol assay were used for assessing a-Smooth Actin (SMA) expression and collagen production, respectively. RNA messenger and protein levels of p100 isoforms were evaluated by QRT-PCR and western blot analysis, respectively.

Here we show that LY294002 was able to abrogate the TGF-β1-induced increase in cell proliferation, α-SMA expression and collagen production besides to inhibit Akt phosphorylation, thus demonstrating the central role of PI3K/Akt pathway in TGF-β1-induced lung fibroblast proliferation and differentiation. Moreover, we show that PI3K p110δ and p100α are functionally expressed in human lung fibroblasts, in addition to the ubiquitously expressed p100β and p100γ. Finally, we demonstrated that Twist nuclear translocation by p100γ and p110δ in the fibrotic process.

Overall, these results suggest that specific class I PI3K isoforms can be pharmacological targets in IPF.

P2006
Inhibition of TGF-β1-induced extracellular matrix production in primary human pulmonary fibroblasts by rapamycin

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Fibroblasts proliferation and extracellular matrix (ECM) accumulation play a key role in the development and the progression of pulmonary fibrosis. Rapamycin has been showed to decrease extracellular matrix in normal mesangial cells and human lung fibroblasts. This study is to examine the role of rapamycin on transforming growth factor β1 (TGF-β1)-induced lung fibrosis and to determine the related mTOR signaling pathways in primary human pulmonary fibroblasts. Primary human pulmonary fibroblasts were isolated from healthy lung transplantation donors. Growth arrested, synchronized cells were treated with TGF-β1 (10ng/ml) and various concentrations rapamycin (0.01, 0.1, 1, 10ng/ml) for 24h. mTOR, p-mTOR, S6K1 and p-S6K1 were assessed by Western blot analysis, type III collagen and fibronectin secretion detected by ELISA, assay III collagen and fibronectin mRNA level determined by Realtime-PCR assay. TGF-β1 (10ng/ml) increased type III collagen, fibronectin secretion and mRNA level obviously compared to controls (p<0.05), rapamycin reduced the enhanced production of type III collagen, fibronectin mRNA and protein induced by TGF-β1 accompanying inhibition of S6K and mTOR phosphorylation. These data demonstrated that rapamycin inhibited TGF-β1-induced type III collagen fibronectin mRNA and protein may be through mTOR/p70S6K pathway, rapamycin may have potential effect for being used in the treatment of pulmonary fibrosis.

P2007
Familial cases of idiopathic pulmonary fibrosis: Clinical observation

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Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, often fatal interstitial lung disease of unknown etiology. Familial idiopathic pulmonary fibrosis (FIPF) is defined when two or more affected individuals are identified in one family. IPF patients accounts for 5.2-2% of all IPF cases.

Results: We found 10 FIPF patients in 5 families among totally observed 475 IPF cases. There were 3 pairs of siblings (2 males and 4 females) and 2 pairs of mother and daughter. Fifteen of 475 IPF patients were diagnosed according to ATS/ERS criteria, histologically proven in 9 of 10 subjects. The mean age of IPF manifestation appears to be 56±9 years; M:F=3:9. Although all lungs showed metastasis, the score of squamous (p=0.001), cuboidal (p=0.018) and bronchial cell (p=0.001) formation of squamous was significantly higher in the “cancer” than in the “no cancer”, while the squamous cell score was similar in the two groups. In conclusion, contrary to previous reports, we have found that the presence of squamous cells, specially squamous, in the honeycombed areas, is associated to the development of precancerous changes in IPF, independently to smoking history.

Idiopathic pulmonary fibrosis (IPF) is known to be associated with increased risk of lung cancer, and are more likely to develop lung cancer than the general population. Several studies have shown that the risk of lung cancer is increased in patients with IPF, with a reported risk of 1.5%-5%.

Conclusion: Familial IPF patients have familial history of pulmonary fibrosis. Although rare, such cases represent an important subgroup in which genetic susceptibility to lung fibrosis plays a significant role. We can use these results to improve our understanding of the pathogenic mechanisms of IPF.

P2008
Paraoquat-induced epithelial-mesenchymal transition: Role of Rac1/beta/ Twist

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Objective: To examine whether paraquat (PQ), a well-known reactive oxygen species (ROS) producer, could induce epithelial-mesenchymal transition (EMT) which involving in ROS-mediated pulmonary fibrosis and possible mechanisms.

Method: Human alveolar epithelial (A549) cells were cultured and exposed to sub-lethal doses of PQ, specific signaling pathway inhibitors and siRNAs for ROS signaling pathway. Intracellular ROS was measured with DCF-DA. Protein and mRNA were evaluated by Western blot and real-time PCR, respectively.

Results: Intracellular ROS increased after various concentration paraquat stimulation for 5 minutes (p<0.05), while only PQ at the concentration of 2μM (PQ20) induced EMT manifested as increased fibroactin, decreased E-cadherin and a fibroblast-like cell appearance. mRNA of Twist, a key transcriptional factor for EMT, increased after PQ20 stimulus for 30minutes (p<0.05), accompanied with a parallel increased Twist nuclear translocation of cells, while transfected with Twist siRNA ant-sense vector abolished PQ-induced EMT. Mitochondrial complex I inhibitor rotenone significantly inhibited PQ20-induced ROS. Small GTPase Rac1 binding in mitochondrial ROS-mediated EMT was induced 5 minutes after PQ20 treatment, and siRNA targeted Rac1 blocked ROS generation and Akt phosphorylation induced by PQ20 (p<0.05). In addition, wortmannin, a PI3K inhibitor, could also block Akt phosphorylation and significantly reduce Twist nuclear translocation in A549 cells 2 hours after PQ20 treatment.

Conclusion: This study demonstrated that PQ could induce A549 cells EMT through Twist up-regulation, which relied on Rac1-dependent ROS generation/Akt signaling pathway and provided a better understanding of pulmonary fibrosis.

P2009
The prevalence of neoplastic transformation in idiopathic pulmonary fibrosis (IPF) lungs. A report from a transplanted IPF population

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Idiopathic pulmonary fibrosis (IPF) is known to be associated with increased risk of lung cancer, with a reported risk of 1.5%-5%.

Conclusion: Familial IPF patients have familial history of pulmonary fibrosis. Although rare, such cases represent an important subgroup in which genetic susceptibility to lung fibrosis plays a significant role. We can use these results to improve our understanding of the pathogenic mechanisms of IPF.
247. Advances in lung function testing from infancy to adulthood

P2010
Lung growth and ventilation inhomogeneity in health
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Lung clearance index (LCI), a measure of ventilation inhomogeneity derived from multiple breath washout is more sensitive in detecting early lung disease than spirometry in preschool (PS) and school age (SA) children. In health, LCI appears to be stable in PS and SA children, but has been reported to be slightly higher during infancy. We aimed to develop a reference range for LCI from birth to 19y.

Methods: LCI data from two centres using a respiratory mass spectrometer (Annis 2000) & the inert gas SF6, measured using either a mask (0.5y) or mouthpiece (>5y), while supine (infant) or seated, were collated. 485 datasets from 359 healthy subjects (443/boys; 257 from London; 102 from Gotteborg; Range: age (0.1-18.7y); height (52-196cm) were analysed.

Results: Height & age were significant predictors of LCI on univariable & multivariable analyses. Mean (SD) LCI was 7.2 (0.5) in infants (0.1-2y); 6.7 (0.6) in PS (3-5y); 6.5 (0.5) in SA (6-12y) and 6.5 (0.5) in those >13y. The inverse relationships between LCI & height or age were not linear, being most marked in the younger years & no longer significant by SA.

Conclusions: LCI was not significantly different between centres, after adjusting for height & age.

P2011
Specific airway resistance is overestimated during tidal breathing vs panting in healthy children
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Rationale: Modern plethysmographic equipments allow the measurement of specific airway resistance (sRaw) during tidal breathing (tb), a potentially useful technique in children unable to perform the panting maneuver (p), a reference technique to minimize the thermal artifact. Equipment softwares are implemented with algorithms to correct for this artifact when computing sRaw. It is not known how well this correction performs with reference to sRawp in children.

Aim: To examine the relationship between sRaw & sRawp in children.

Methods: sRaw and sRawp were measured in 6 healthy children aged 7-10 years, using a commercially available pressure plethysmograph. Results: sRawp (mean ± sd = 10.4±2.0 hPa sec/L; breathing rate = 0.5±0.1 Hz) was significantly larger (p=0.006) than sRawp (5.8±2.2 hPa sec/L; breathing rate = 3.1±0.5 Hz). The finding hold true for Raw computed from the associated measurement of thoracic gas volume (Rawth = 6.3±1.2 hPa sec/L; Raw = 2.9±1.0 hPa sec/L; p=0.005).

Conclusion: sRaw is significantly overestimated by tb as compared with p. This is possibly explained by non instantaneous changes of gas temperature and humidity in the airways, a fact that may not be taken into account in the correction algorithm. The impact of overestimating Rawtb’s and hence Raw - on routine airway function testing in patients has to be identified.
but between-subject variability increased with growth (Fig. 1a,b). 95% Limits based on V50g or Cr50g would over-estimate predicted range in the youngest and under-estimate it in older infants, leading to potential misdiagnosis. V50g or Cr50g were inversely related to weight z-score (Fig. 1c,d); light-for-age babies had higher values than those who were heavier. This again may lead to misdiagnosis especially in those with impaired growth (ef. CF).

Conclusions: Reporting infant LF/kg body weight is inappropriate. Equipment-specific regression equations are needed to avoid misinterpretation; for this a larger dataset is required. We would welcome contributions of similar data from other centres.

P2014 Tracking of lung function obtained by whole-body plethysmography in infants and children with cystic fibrosis (CF)

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Rationale: The assessment of lung function tracking, (data stability over time and prone by age) based on early measurements could contribute to a better understanding how genetic and environmental factors as well as treatment regimens influence lung function decline in CF.


Methods: Lung function was assessed in 70 infants (35 males, 35 females) with CF at ages 2.8 to 26.7 months as well as during childhood (4.3-18.4 years) by serial (infant)-whole-body plethysmography pertaining to functional residual capacity (FRCpleth) and effective airway resistance (sReff). Using predicted values obtained by LMS statistics (see abstract 854139), z-scores of FRCpleth and sReff were computed by Box-Cox transformation using the age-varying parameters L (skewness), M (median) and S (coefficient of variation).

Results: During infancy only 7.6% of CF patients presented with normal lung function; 33.3% showed either pulmonary hyperinflation or bronchial obstruction, but 59.1% presented with both. There was a significant association with later outcome represented by the LC1 und the FEF50. If genotypes are stratified according to the presence or absence of F508del and subgrouped according to the nature of mutations, FRCpleth and sReff can achieve discrimination.

Conclusions: Evaluation of lung function by plethysmography is an important diagnostic and predictive tool, featuring good outcome parameters, and worth to be established early in life.

P2015 Pressure oscillations after airway interruption pre- and post-bronchodilator in wheezy preschool children

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Changes in mouth pressure during flow interruption (Pmno transients) can be used to assess airway resistance (Rint). Initial pressure oscillations can cause difficulties in estimating Rint but are themselves a marker of a airway status as their amplitude increases [1] with bronchodilator (BD) and decreases with methacholine [2]. To investigate this measurement, we analysed Pmno transients pre- and post- bronchodilator in 13 preschool children with recurrent wheeze on 2 separate visits 4 weeks apart. The median (range) age of the children at the first visit was 52 months (38 to 64 months). The amplitude of the first upward oscillation as a proportion of end-expiration pressure was calculated and compared with Rint calculated by linear back extrapolation. The median value of at least 5 acceptable transients was determined for each one.

To investigate this, we analysed Pmno transients pre- and post- bronchodilator in 13 preschool children with recurrent wheeze on 2 separate visits 4 weeks apart. The median (range) age of the children at the first visit was 52 months (38 to 64 months). The amplitude of the first upward oscillation as a proportion of end-expiration pressure was calculated and compared with Rint calculated by linear back extrapolation. The median value of at least 5 acceptable transients was determined for each one.

Conclusions: Evaluation of lung function by plethysmography is an important diagnostic and predictive tool, featuring good outcome parameters, and worth to be established early in life.

P2016 Cough flow volume profile in ataxia telangiectasia

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4The Pediatric Pulmonary Unit and Ataxia Telangiectasia National Clinic, The Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Affiliated with the Sacker Faculty of Medicine, Tel-Aviv University, Ramat-Gan, Israel

Introduction: Weak coughing is perceived as the cause for recurrent respiratory system infection leading to lung function deterioration in Ataxia telangiectasia (A-T) disease. The cough profile of these patients has not been studied.

Aim: To explore the feasibility of the cough-flow-volume profile for detecting cough performance in A-T patients.

Methods: Thirty five A-T patients (age 12.7±4.9yrs) were studied. Patients performed forced expiratory flow volume (FVC) and maximal voluntary cough (FVC-cough) maneuvers. Analysis of data included: Inspiratory volume (IC) prior to cough, FVC-cough, Peak cough flow and number of spikes per maneuver. Values were related to published data of healthy population of similar ages and are presented as actual and as%predicted.

Results: We found that IC prior to cough was 0.85±0.47 l (36.1±15.0%); FVC-cough was 1.00±0.51 l (43.6±15.4%); Peak cough flow was 3.27±1.53 l/s (45.5±15.0%); Peak cough flow to Peak expiratory flow ratio was 1.06±0.24 vs 1.48±0.22 in healthy and the number of spikes/maneuver were 2±0.68 vs 6±12 in healthy population. All parameters were significantly lower than healthy (P<0.001). Additionally, Peak cough flow increased with age but the yearly increase rate was significantly lower than normal, (0.157 vs. 0.423 l/year; respectively, P<0.05).

Conclusions: Our findings indicate that A-T patients have a weak cough compared to healthy of similar ages and that cough ability worsens with age. Cough flow volume curve, as well as forced vital capacity maneuvers, should be considered a mainstay in the clinical assessment of A-T patients. The study was funded by the J. Baum foundation of the Israeli Lung Association, Tel Aviv, Israel.

P2017 The maximum oxygen consumption in children with asthma and/or obese children: A multi purpose assessment

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Aim: Asthma and obesity have had an increasing trend in recent decades, constituting one of the major priorities in the health of children. The aim of this study was to compare the respiratory function and oxygen consumption in four groups of children: obese, asthmatics, obese-asthmatic and controls, in order to assess their metabolic pattern and respiratory values.

Methods: 152 children, 8 to 16 y.o., divided as follows: 31 asthmatics, 42 controls, 56 obese and 23 obese-asthmatics children were tested. Every child performed spirometry, respiratory muscles (endurance) and oxygen consumption (VO2) evaluation, obtained on a cycloergometer according to a protocol of increasing effort.

Results: Spirometric values were comparable between obese and controls (average: FVC 105 and 107% pred, respectively), whereas there was a s.s. difference (P<0.05) between asthmatics and obese-asthmatics. Endurance was lower in obese (26.97 l) and obese-asthmatics (24.06 l) than in asthmatics alone (31.52 J) and controls (31.98 J), but without any s.s.difference (p=0.60). The maximal VO2 was lower in obese (30.63 ml/kg/min) and obese-asthmatics (31.95 ml/kg/min) than in controls (37.19 ml/kg/min) or asthmatics (41.72 ml/kg/min) (p=0.001 for each one).

Conclusion: The increase in body weight does not seem to affect spirometric values but obese children have a lower value of endurance, probably due to a respiratory muscle weakness and VO2/kg max was lower in obese than asthmatics, probably due to alterations in the cardio respiratory system.

P2018 Exercise induced bronchoconstriction and dyspnoea in asthmatic children

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Introduction: Dyspnoea is thought to signal the mismatch between afferent input arising from the respiratory system and metabolic needs. Dyspnoea is thought to signal the mismatch between afferent input arising from the respiratory system and metabolic needs. Dyspnoea is thought to signal the mismatch between afferent input arising from the respiratory system and metabolic needs. Dyspnoea is thought to signal the mismatch between afferent input arising from the respiratory system and metabolic needs. Dyspnoea is thought to signal the mismatch between afferent input arising from the respiratory system and metabolic needs.

Dyspnoea is induced by airway obstruction but is variably expressed. A poor perception of dyspnoea has been hypothesized to be a determinant factor to life threatening asthma.

Methods: 53 asthmatic children (6 - 16 years old) were studied at baseline and 5 min after exercise. Dyspnoea was rated qualitatively and quantitatively by the...
pediatric scale “Pictorial-CERT” (ΔSc = 0 to 10). EIB was assessed by the relative change in FEV1 (ΔFEV1) and the child classified as responder (R) or nonresponder (NR) based on a threshold decrease in FEV1 = 8%.

Results: Anthropometric characteristics and baseline FEV1 were similar in R’s and NR’s. The qualitative items “Pictorial-CERT”, “Pictorial-CERT” and “Pictorial-CERT” were more frequently quoted by R’s than NR’s (p < 0.05). There was a significant but loose correlation between ΔFEV1 and ΔSc (r² = 0.12; p < 0.001).

Eight subjects were identified as poor perceivers because of significant bronchoconstriction contrasting with ΔSc < 2. These subgroup characteristics were similar to other children.

Conclusion: Bronchoconstriction and perception of dyspnoea are significantly but weakly associated in asthmatic children. Some children exhibit a poor perception of EIB. A systematic evaluation of dyspnoea during exercise challenge may help in the screening of subjects at risk of life-threatening asthma.

P2019 Agreement between interrupter resistance and spirometry in a large population of asthmatic children
Nicole Beydon1, Bruno Mahar1, Maingot Lucia1, Houa Guillo1, Marie-Claude La Rocca1, Noria Medjahid1, Marc Koskas1, Michèle Bouil1, Christophe Deleclaux2, 1Lung Function Department, Armand Trousseau Hospital, Paris, France; 2Lung Function Department, Georges Pompidou European Hospital, Paris, France

Background: Interrupter resistance (Rint) is routinely used to assess airway patency in children, but its relationship with spirometry has never been assessed in a large population of children.

Objectives: A retrospective study to compare baseline values and post-bronchodilator (post-BID) changes in Rint and spirometry in asthmatic children.

Methods: Rint measures (SpireDry R, Dry R, France) were performed before spirometry (Masterscreen, Jaeger, Germany). Statistics: correlations between baseline Rint and FEV1 or FEF25/75%, and ROC study for the Rint cutoff to distinguish between children with and without reversibility in FEV1 (>12% baseline).

Results: Data from 645 children (408 boys, median (range) age 7.9 (4.2-18.3) y) showed significant correlations between Rint and FEV1 or FEF25/75% (r=0.69 and 0.71, respectively for raw data, and r=0.49 and 0.54, respectively for% of predicted; all p<0.0001).

Figure 1
Reversibility in FEV1 (270 children) was best detected by a -35% of predicted Rint decrease (AUC=0.79, 0.70 sensitivity and specificity).

Abstract P2021 – Table 1

<table>
<thead>
<tr>
<th>M</th>
<th>L</th>
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</thead>
<tbody>
<tr>
<td>Boys</td>
<td>127.77 + 162.52 + age</td>
</tr>
<tr>
<td>Girls</td>
<td>128.42 + 167.91 + age</td>
</tr>
</tbody>
</table>

Conclusion: We found a good agreement between Rint and spirometry to assess airway calibre and study BDeffect.

P2020 Bench test of an O2/CO2 sensor based MBW system using a lung model
Florian Singer1, Chiara Abba1, Emilia Wluk1, Paul Robinson2, Philipp Latzin1, Per Gustafsson1; 1Division of Pulmonology, Department of Pediatrics, University Children’s Hospital, University of Bern, Bern, Switzerland; 2Division of Pulmonology, Department of Pediatrics, Central Hospital, Skeoede, Sweden; 3Department of Pediatrics, The Children’s Hospital at Westmead, Westmead, Australia

Lung volume assessment using tracer gas multiple breath washout (MBW) systems needs validation under realistic conditions. We used a lung model allowing for different tidal volumes (TVs), functional residual capacities (FRCs), and respiratory rates (RRs) under BTPS conditions. We tested a nitrogen (N₂) MBW prototype (Exhalyzer D; Eco Medics) based on an ultrasonic flowmeter, a main-stream CO₂ and a side-stream O₂ sensor.

Linearity of O₂ and CO₂ sensors was assessed after two point calibration using a mass spectrometer (AMIS 2000; Innovision). For FRC measurements, a double chamber plexiglas lung model was filled with water, heated, and mechanically ventilated at various ranges of FRCs (900 to 4000 mL), TVs (250 to 850 mL), and RRs (30 to 15/min). N₂ MBW tests (n = 71) using 100% O₂ were done on three days. Using custom designed software (TestPoint) we synchronized gas to flow signals to preset and manually optimized settings, and calculated FRC as cumulative expired N₂ volume divided by the difference of MBW start minus end N₂ concentration.

O₂ and CO₂ sensors were linear (linear regression r² was 0.99 for both). Using preset synchronization settings, mean difference of lung model minus measured FRCs was -7.4 mL (-0.4% of mean FRC), limits of agreement ranged from 160.4 mL to -175.2 mL (5.8% to -5.9% of mean FRC). After optimized synchronization, mean difference of FRCs was -7.7 mL (-0.25% of mean FRC); limits of agreement ranged from 50.8 mL to -66.2 mL (1.8% to -2.3% of mean FRC). This lung model seems suitable for validation of MBW systems. The new N₂ MBW system precisely measures in vitro FRCs under realistic conditions. Careful synchronization of signals is crucial for accurate FRC measurements.

P2021 Reference data transition of whole-body plethysmography from infancy to childhood
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Rationale: Advances in plethysmographic measurement techniques have made it possible to obtain lung function data in infants [1] and children. However, application remains limited by the lack of appropriate transitional normative data from infancy to childhood, especially for effective specific airway resistance (sReff).

Objectives: On previously collected lung function data, updated prediction equations were modeled spanning from infant’s years to childhood, using the LMS method.

Methods: Normative lung function data from 67 healthy young infants aged 2.3 to 28.2 (10.8±6.3) months and children aged 5.1 to 16.8 (10.4±2.9) years were evaluated, and prediction equations for functional residual capacity (FRCpleth), and sReff were computed. Applying the LMS method in R environment using GAMLSS package [2] the changing distribution of the measurements is summarized by three curves representing the median (M), coefficient of variation (S) and skewness (L) in relation to age.

Results: The present prediction equations feature the first attempt to provide continuous normative data of infants with a smooth transition into childhood (Table 1).

Conclusions: Updated prediction equations of plethysmographic data for infants and children applying LMS statistics provide a new basis for longitudinal evaluation of lung function in children with lung disease.

References:

MONDAY, SEPTEMBER 26TH 2011

353s

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P2022

Comparison of a new nitrogen multiple breath washout method to mass spectrometer SF6 washout in cystic fibrosis subjects

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Background: The lung clearance index (LCI) obtained from SF6 multiple breath washout (MBW) is a sensitive index of peripheral airway dysfunction in cystic fibrosis (CF) [1]. SF6 LCI values are lower and show stronger agreement between laboratories than historical N2 LCI using conventional N2 analysers [1]. Formal comparison between the two types of MBW systems has not been performed to date. This study compared FRC and LCI obtained using both methods: mass spectrometer SF6 MBW and a new indirect N2 MBW system (Exhalyser D, EcoMedics, Daumen, Switzerland) in CF subjects.

Methods: 10 CF subjects, median (range) 17 (15 -40) yrs performed MBW in triplicate using an SF6-based mass spectrometer MBW system and an Exhalyser D indirect N2-based MBW system (main stream infrared CO2 sensor, side stream laser O2 sensor). FRC and LCI were calculated using similar software algorithms. Results expressed as mean (SD) and between-test comparisons made using students t-tests.

Results: There was no significant difference between FRC values (N2 FRC 2.82 (0.71) vs. SF6 FRC 2.53 (0.70), p=0.37), however N2 LCI 12.52 (3.14), was significantly higher than SF6 LCI 9.77 (2.46) (p=0.043). Within-session repeatability (coefficient of variation, CV%) did not differ between the groups: N2 FRC 6.3 (2.9%) vs. SF6 FRC 5.5 (3.1%), and N2 LCI CV 5.0 (3.6%) vs. SF6 LCI CV 4.7 (2.8%).

Conclusions: LCI values obtained with the new indirect N2 MBW system were greater than those obtained with the current gold standard SF6 mass spectrometer based system. FRC values and within-session repeatability were similar.

References:

P2023

Excluding extreme breaths from analysis can change conductive airway ventilatory inhomogeneity by over 25% in cystic fibrosis

Noor Al-Khalfan 1, Ruslan Garpr 3, John Owers-Bradley 4, Erol Gaillard 1, 2, Carl-Robert Bergstrom 1, 4, 5, 6, 7.

Background: Airway inhomogeneity (VI) and separating healthy from CF children despite considerable overlap. More detailed analyses are needed to better understand underlying pathophysiological phenomena and to obtain additional yet unknown information on VI from this test.

Methods: We performed multi-breath nitrogen washout in 16 children with CF aged 6 -17 yr. An auditory signal indicated when the child has inspired a pre-set tidal volume (Vt) of the breath has been used as a correction. Slopes (SnIII) allows differentiation of inhomogeneity of conducting and acinar airways (Scond and Sasin). Standardising data collection and analysis in subjects with recent symptoms in young children with asthma.

Results: We identified double tracer gas SBW indices reliably characterizing ventilation inhomogeneity (VI) and separating healthy from CF children despite considerable overlap. More detailed analyses are needed to better understand underlying pathophysiological phenomena and to obtain additional yet unknown information on VI from this test.

References:

P2026

Relationship between lung function using forced oscillation technique (FOT) with recent symptoms in young children with asthma

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Background: Use of FOT to assess lung function in young children is increasingly reported in the clinical setting. However, associations between bronchodilator responsiveness (BDR) as assessed by FOT and recent symptoms in young children with asthma have not been reported. We aimed to investigate the relationships between recent respiratory symptoms and BDR using FOT in young children with asthma.

Methods: 70 children (aged 3 to 6y) with mild asthma were studied twice 5 months apart. FOT (resistance and reactance at 8Hz: Rrs8 and Xrs8, respectively) was measured prior to- and 15 mins following Salbutamol (600 μg) inhalation. The BDR was assessed using absolute and relative changes in Rrs8 and Xrs8. Respiratory symptoms in the month prior to each visit were obtained using daily diary card. We performed regression analyses assessing the impact of respiratory symptoms on the transformed absolute and relative BDR in Rrs8 and Xrs8.

Results: Pre- and post-BD Rrs8 and Xrs8 data were obtained from 70 children at visit 1, and 56 children at visit 2. There were no differences in BDR for Rrs8 with any reported symptoms. In contrast, Xrs8 BDR was significantly larger (p<0.05)
in children reporting wheeze that required relievers in the month prior to FOT testing.

Conclusions: In children with mild asthma increasing symptom incidence requiring reliever use is associated with an increased BDR in Xer.8 These data suggest that symptoms in early childhood asthma result in alterations in peripheral airways function. Alternatively, it may indicate that the FOT is poorly sensitive to asthma related lung disease in young children. Further research addressing this question is required.

P2027
In vitro validation of nitrogen multiple breath washout using ultrasonic equipment
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Over the last years, ultrasonic equipment for Multiple Breath Washout (MBW) including measurement of functional residual capacity (FRC) and assessment of ventilation inhomogeneity has been developed (EasyOne Pro, ndd Medizintechnik AG, Switzerland). Accuracy of the ultrasonic flow sensor has been demonstrated against mass spectrometry. Validity and feasibility have been demonstrated in single and in multi-centre studies using SF6 as the tracer gas. Recently, the washout procedure has been changed to nitrogen washout. All analysis steps, including delay correction between flow and side-stream molar mass signals were automated to facilitate clinical use. However, calculation of both, FRC and parameters of ventilation homogeneity depend on accuracy of the underlying algorithms. The aim of the present study was to assess the accuracy of the EasyOnePro software for calculating FRC from nitrogen MBW using a novel lung model. The lung model consists of an inner and an outer water-filled Plexiglas chamber (Soloplex AB, Sweden) and is driven by a mechanical ventilator (Evita, Dräger, Germany); the water level of the inner chamber, which is partially separated by a wall to allow ventilation, determines the target FRC. 60 measurements were performed using FRC target volumes between 350 and 4000 ml. Respiratory rates were set between 10 and 20 min⁻¹ and tidal volumes between 300 and 800 ml. Within-test repeatability of three measurements was below 0.76% for all settings. Mean difference between target FRC and measured FRC was 3.28% (95% CI -45 ml; -31 ml). We conclude that the Easy One Pro Software accurately calculates FRC.

248. Acute respiratory failure

P2028
Comparison between the transcutaneous carbon dioxide tension at the infraclavicular site with the arterial carbon dioxide tension
Prashant Chhajed1,2, Parag Chaudhari 1,2, Chandrashekar Tulasi giri3, Arvind Kate1,2, Rajendra Kesawari1, Josep Loup 1, Florent Bory1,2, Lung Care & Sleep Centre, Institute of Pulmonology, Medical Research and Development, Mumbai, Maharashtra, India; 1Lung Care and Sleep Centre, Fortis-Hiranandani Hospital, NaviMumbai, Maharashtra, India; 2Critical Care, Fortis-Hiranandani Hospital, NaviMumbai, Maharashtra, India

Background: Transcutaneous measurement of carbon dioxide is routinely done at the earlobe site. In patients receiving non invasive ventilation or in the intensive care setting with necklines, an alternate measurement site would be useful. The infraclavicular site has major blood vessels in its vicinity. We started to use the infraclavicular site for transcutaneous measurements of carbon dioxide using a new digital sensor.

Aim: Comparison of transcutaneous carbon dioxide with arterial carbon dioxide at the infraclavicular site.

Methods: We retrospectively compared transcutaneous carbon dioxide at the infraclavicular site with arterial carbon dioxide in 50 samples. The Sentec Digital Monitoring System (SentecAG, Thewil, Switzerland) was used. The V-Sign digital sensor was placed on the infraclavicular site at the medial two third and one fifth point from the sternoclavicular joint and acromioclavicular joint.

Results: When comparing PtCO2 with PaCO2 values, the Bland-Altman analysis revealed a bias of 0.15 mmHg (95% CI: ±0.76; 1.05) with a precision of 3.18 mmHg. Linear regression analysis describes the relationship between the two methods. The slope of the linear model was 0.85 ± 0.04 and the intercept was 5.78 ± 1.58 (RSE = 2.8, R² = 0.91).

Conclusion: The measurement of transcutaneous carbon dioxide at the infraclavicular site is feasible with a digital sensor and has a good correlation with the carbon dioxide values obtained from the arterial blood gas.

P2029
Post operative surgical patients can be successfully managed using the target oxygen saturation scheme with the BTS emergency oxygen guidance
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Too little and too much oxygen can both prove fatal. The BTS Guideline for Emergency Oxygen used in adults patients was published in 2008. The essence of the guideline was that oxygen is prescribed according to a target saturation range and the patients subsequently be kept within the target range. The target saturation could be used in the post operative period although this was not covered in detail in the guideline. In this hospital, Anaesthetists prescribe oxygen post-operatively to target saturation. This study investigated whether this is successful.

Methods: 49 patients were studied in the post-operative ward and in the surgical ward to examine whether the BTS guideline was being followed.

Results: All patients had been prescribed oxygen to a target saturation of 94-98%. Patients on the post operative ward from 45-90 minutes. Saturations were checked every 15 minutes on all patients. Only 3 saturations were below 94% and all were on the initial recording in the post op ward. The oxygen saturation was above 98% in 30 of the 42 patients on oxygen at 15 minutes and 24/40 at 30 minutes. At 60 minutes on the post op ward, 6 patients were on nasal seps (N5), 24 on simple face masks (SM) on arrival on the surgical ward, 16 were on NS and 2 were on SM. In 25 oxygen had been stopped and there was no data on 6 patients. In 6 patients on SM the flow was reduced below 5 L/min. Re-breathing may occur and this is not recommended.

Conclusion: The BTS Emergency Oxygen Guideline the target saturations can be successfully used in post operative surgical patients. Low oxygen saturations were rare but high saturations were common.

P2030
Continuous intraarterial blood pH monitoring in rabbits with acid base disorders
Weizhong Jia1, Jianjun Jiang, Yuanlin Song, Chunxue Bai, Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai, China

Acid-base balance of arterial blood is important in clinical management of seriously ill patients, especially in patients with acute lung injury or acute respiratory distress syndrome. We developed a novel fluorosensor for continuous blood pH monitoring and evaluated its performance both in vivo and in vitro in rabbits with acid-base disorders. The pH sensor is made of N-Allyl-4-piperazinyl-1, 8-naphthalimide and 2-Hydroxyethyl methacrylate, which were bonded at the distal end of the optical fiber.

The fluorescence intensity increased as the pH decreased with good reproducibility, selectivity and linearity in the pH range of 6.8 – 7.8.
The pH measurement accuracy was -0.00±0.1 pH units (n=189) in rabbits with respiratory acid-base orders. The optical pH sensor can accurately measure pH fluctuations with fast response and is a promising candidate for continuous inline measurement of blood pH in critical care patients.

P2031
A preliminary study of the prevalence of hypoxaemia, hyperoxaemia, hypercapnia and acidosis in hospital blood gas specimens
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1Respiratory Medicine, Salford Royal University Hospital, Salford, UK; 2Biochemistry, Salford Royal University Hospital, Salford, UK

Over or under treatment of hypoxaemia can be dangerous. We studied 3524 blood gas specimens at a university hospital. 362 samples (10.2%) were hypercapnic with oxygen saturation below 90% and 2.7% were severely hypoxaemic with saturation below 80%. 1074 samples (30%) were hyperoxaemic with PaO2 > 15.0 kPa. This study shows that these were under-recognized conditions in hospital practice and is usually associated with respiratory rather than metabolic acidosis. Hyperoxaemia (30% of samples), hypercapnia (27% of samples) and respiratory acidosis (21% of samples) were relatively common. This suggests that oxygen needs to be used more with caution in hospitals in the light of recent studies showing increased mortality associated with hyperoxaemia in a range of common clinical conditions.

P2032
Acoustic respiratory monitoring (ARM) of wheeze (Wz) and cough (C) in the pediatric emergency department (PED)
Sigmund Kharasch1, Alex Gileles-Hillel1, Ibrahim Omar1, Virginia Kharasch1, Eitan Kerem1, 2Pediatrics, Hadassah-Mount Scopus, Jerusalem, Israel; 1Critical Care, Children’s Hospital, Boston, MA, United States

Background: Wz and C are common in the PED, but are only assessed qualitatively and intermittently. We evaluated the feasibility of quantitative ARM in noisy PED.

Methods: 11 PED dyspea patients (7m-1y) were monitored by ARM (PalmoTrack® KarmelSonix, Israel) using 2 PPG sensors, an effort belt and an ambient microphone (MIC). WheezeRATE® (Wz%), quantified as the Wz duration (% of the elapsed time) and CoughCOUNTER® (CC) were continuously measured.

Results: Recordings of all 11 patients generated usable data (t=146 min, 93-314 min) with good ambient noise rejection. 5 patients had bronchiolitis (BR), 3 asthma (AS), 2 pneumonia and 1 cough-variant asthma (C-Va). CC was the most prominent feature with 10/11 patients having CC. A transient reduction of CC occurred after hypertonic Saline in 2/5 BR patients, after ventoline in 1/3 AS and in 1/3 C-Va patients. Wz% was elevated in 2/5 BR and 2/3 AS patients. In one patient the belt signal was poor and in one patient there was a transient disconnect of the MIC resulting in false detection of ambient noises as Wz.

Discussion and conclusions: We found that high CC is the most common sign in patients with dyspnea and that CC reduction in response to therapy provided valuable clinical information. Continuous ARM of wheeze and cough is feasible in a noisy PED. Monitoring a larger population is needed to fully assess the clinical value of ARM in the PED.

Acknowledgement: S Godfrey, N Gaviely and E Balouka from KarmelSonix assisted in data recording and analysis.

P2033
The use of plasma n-terminal pro B-type natriuretic peptide (proBNP) concentrations in differential diagnosis of comorbidity pulmonary patients
Periet Kajuyo1, Dhimrait Arjirgi1, Anila Mitre2, Jeta Beki1, Amila Alliko1, Elena Shehu1, Roland Kore1, Ylli Vakeflliu1, Holta Tafa1
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Study objective: The use of plasma proBNP concentrations as a diagnostic tool in differential diagnosis of dyspnea in comorbidity pulmonary patients.

Abstract P2033 – Table 1. Summary of blood gas results grouped according to oxygen saturation levels

<table>
<thead>
<tr>
<th>Oxygen saturation range</th>
<th>Number of samples</th>
<th>Percent of samples</th>
<th>Number (percent) hypercapnic</th>
<th>Number (percent) uncompensated respiratory acidosis</th>
<th>Number (percent) uncompensated respiratory acidosis</th>
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<tr>
<td>&gt;98%</td>
<td>1458</td>
<td>41.3%</td>
<td>305 (21%)</td>
<td>83 (6%)</td>
<td>161 (11%)</td>
</tr>
<tr>
<td>94–98%</td>
<td>1291</td>
<td>36.6%</td>
<td>294 (23%)</td>
<td>65 (5%)</td>
<td>167 (13%)</td>
</tr>
<tr>
<td>92.1–93.9%</td>
<td>237</td>
<td>6.7%</td>
<td>85 (36%)</td>
<td>14 (6%)</td>
<td>58 (24%)</td>
</tr>
<tr>
<td>88–82%</td>
<td>288</td>
<td>8.2%</td>
<td>119 (41%)</td>
<td>35 (12%)</td>
<td>61 (21%)</td>
</tr>
<tr>
<td>80–79.9%</td>
<td>154</td>
<td>4.3%</td>
<td>76 (49%)</td>
<td>18 (12%)</td>
<td>41 (27%)</td>
</tr>
<tr>
<td>70–79.9%</td>
<td>53</td>
<td>1.5%</td>
<td>40 (75%)</td>
<td>12 (23%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>60–69.9%</td>
<td>22</td>
<td>0.6%</td>
<td>14 (64%)</td>
<td>6 (27%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>&lt;60%</td>
<td>21</td>
<td>0.6%</td>
<td>6 (29%)</td>
<td>5 (24%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>3524</td>
<td>100%</td>
<td>948 (26.9%)</td>
<td>239 (6.8%)</td>
<td>518 (14.7%)</td>
</tr>
</tbody>
</table>

65 samples had mixed respiratory-metabolic acidosis.

P2035
The causes of hemoptysis and lung hemorrhage in patients with pulmonary sarcoïdosis
Olga Barannova1, Valentina Molodtsova2, Alexandra Speranskaja1
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Study objective: The use of plasma proBNP concentrations as a diagnostic tool in differential diagnosis of dyspnea in comorbidity pulmonary patients.
pulmonary sarcoidosis (PS) modifying the typical clinical and radiological disease picture.

**Aim:** To analyze causes of hemoptysis and lung hemorrhage in PS patients (pts) with the use of modern abilities of radiological assessment (computed tomography - CT, high resolution CT - HRCT, CT with angiography, single photon emission CT - SPECT) and bronchoscopy.

**Methods:** We studied 30 patients (f/m - 17/13) with morphologically confirmed PS with hemoptysis and lung hemorrhage (stages: 1st - 4, 2nd - 9, 3rd - 3, 4th - 5). The average age was 37.2 ± 2.3 years. All patients were subjected to clinical and radiological (HRCT, CT with angiography, SPECT) researches and bronchoscopy.

**Results:** The main causes of this severe complication were pulmonary embolism (17 pts including thrombosis “in situ” in 3 of them) with pulmonary arterial hypertension, atrophic bronchitis (3 pts), traction bronchoceles (3 pts), dry cavities (2 pts), tuberculosis (1 pt). In carrying out bronchography hemoptysis was found in lung tissue viral and bacterial infections (2 pts) and lung cancer (1 pt). The relapsing lung hemorrhage was observed in only one patient with 4 stage PS complicated by micosepsis in thrombotic tissue. In 3 pts bronchoscopy was performed on top of bleeding using various methods of endobronchial hemostasis.

**Conclusion:** Using modern methods of radiological imaging (CT, HRCT, CT with angiography, SPECT) we also were able to detect the main cause of hemoptysis in PS patients - pulmonary embolism including thrombosis “in situ”.

**P2036**

Recognizing fatal pulmonary embolism in young adults with simple clinical measurements

Oxana Tesenko, Alexey Glechikov. Pulmonology, State Academy of Postgraduate Education, Moscow, Russian Federation

**Introduction:** As the incidence of pulmonary embolism (PE) in individuals older than age 45 is higher, numerous studies have shown that in young adults the diagnosis is missed more often than it is made. Death from PE in this group of patients might be considered to be most likely to be preventable. Nowadays there aren’t robust criteria to estimate risk of mortality from PE in young patients.

**Aim:** To identify risk factors of mortality from PE in young people.

**Methods:** We reviewed data from 167 young patients (all male) with PE. Mean age was 44.5 ± 5.2 years. Died. StatSoft Software (version 5.0, 1997) was used for calculations.

**Results:** We analyzed 25 factors of inherited risk (antithrombin III deficiency, protein C and protein S deficiency, factor V Leiden mutation), acquired risk (surgery, malignancy, trauma, obesity, cigarette smoking) and presenting syndromes. Multivariate logistic regression revealed that immobility (bed rest) due to operation or severe disease) (OR 7, 95% CI 3,4–18,9), malignancy (OR 6, 95% CI 2,1–9,2) are forth independent predictors of mortality. (OR 3, 95% CI 2,1–9,2) are forth independent predictors of mortality.

**Conclusion:** The risks of PE are multiple. Although our model requires further validation it may be useful as simple and fast method for identifying young patient with poor prognosis PE and treatment with anticoagulants.

**P2037**

Severe airway response associated with anaphylactic shock in allergic Brown Norway rats

Grégoire Barthel2,3, Bruno Demoulin 1, Chantal Montémont 2, Feng Zheng 2, Severe airway response associated with anaphylactic shock in allergic Brown Norway rats

**Background:** Bronchospasms may occur as part of the early response to anaphylaxis on induction of anesthesia in humans. However, little data are available on the changes in respiratory mechanics occurring in animal models of anaphylactic shock.

The aim of the study was to delineate the respiratory mechanical impedance response to ovalbumin (OVA)-induced anaphylaxis in Brown Norway rats.

**Methods:** Anesthetized, tracheostomized, paralysed and mechanically ventilated ovalbumin-sensitized male Brown Norway rats were randomly allocated to intravenous OVA (n=11) or vehicle (n=7). The respiratory resistance (Rrs) and reactance (Xrs) were measured at 20 Hz using the forced oscillation technique.

**Results:** Allergic rats showed consistent and dramatic increase in respiratory impedance. The peak Rrs response - almost a threefold increase - occurred 49 sec after OVA injection (from 51.2 ± 5.4 to 140.9 ± 5.4 hPa.s/L). Protein C and protein S deficiency, factor V Leiden mutation, acquired risk (surgery, malignancy, trauma, obesity, cigarette smoking) and presenting syndromes. Multivariate logistic regression revealed that immobility (bed rest) due to operation or severe disease) (OR 7, 95% CI 3,4–18,9), malignancy (OR 6, 95% CI 2,1–9,2) are forth independent predictors of mortality. (OR 3, 95% CI 2,1–9,2) are forth independent predictors of mortality.

**Conclusions:** Severe airway obstruction occurs with anaphylactic shock in allergic Brown-Norway rats. The associated decrease in Xrs indicates an increase in apparent respiratory elastance (e.g. with lung vascular engorgement or pulmonary oedema). The inhomogeneity of mechanical time constants within the lung from heterogeneous bronchoconstriction. Data from this animal model emphasize the heterogeneity bronchoconstriction. Recognizing fatal pulmonary embolism in young adults with simple clinical measurements

**P2038**

Follow-up and educational results of bed head lift in intensive care unit

Suat Solmaz, Razaye Sancar, Necile Ornek, Roya Evin, Ozlem Moçın, Emeç Saltukce, Semra Ruki Kafali, Zehra Karkuk. Respiratory Intensive Care Unit, Suryeyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

**Objective:** Lifting head of bed is simplest and most important way to prevent aspiration pneumonia in intensive care unit (ICU). In our study we investigated the contribution of reminding this application.

**Method:** Prospective study was done in 22 bed intensive care unit (ICU) between December 2010-January 2011. None of the staff other than researchers were aware of this observational study. Every day during December 2010 at 8.00 a.m and 5.00 p.m 22 ICU bed head position were recorded whether their heads were 30-45 degrees elevated or straight.During January 2011, nurses responsible for beds were told to lift head bed positions and bed head positions were recorded again. Inflection nurse noted aspiration or ventilator associated pneumonia (VAP) cases every two months. Values were summarized with descriptive method.

**Results:** In December 2010, 1278 in January 2011, 1283 bed head positions were recorded. 26 of total 56 (46.4%) records were done in the morning, 30 were done in the evening during December 2010. In January 2011, 24 of total 41 (51.2%) were done in the morning and 17 in the evening. One patient had VAP and died after 12 days in December 2010. In January 2011, 3 VAP. Aspiration pneumonia were observed and they stayed total 64 days in ICU and one of them was died.

**Conclusion:** Reminding of lifting head bed positions at certain hours, during shift changes reduce inappropriate bed head position. This method which is used in reducing the risk of VAP and aspiration pneumonia, shortens ICU stay, contribute country income, decrease aspiration related mortality.

**P2040**

Successful use of interventional lung assist device in a patient with near fatal asthma

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Interventional lung assist devices (iLA) are pulpless, arterio-venous, extracorporeal lung support devices with a low resistance gas exchange membrane that allows rapid removal of carbon dioxide (CO2) and moderate oxygenation. Currently they are mainly used in acute respiratory distress syndrome and as a bridge to lung transplantation. We successfully used iLA in an 18 year old asthmatic patient with hypercapnic respiratory failure refractory to conventional ventilation. A male patient aged 15 years presented with a near fatal exacerbation of asthma. He had a current smoker with a history of chronic obstructive pulmonary disease affecting right leg, stroke and ischaemic heart disease. Despite full medical treatment, endobronchial intubation and invasive mechanical ventilation (IMV) plus a range of intravenous and inhaled medications including intravenous terbutaline, ketamine, adrenaline and inhaled adrenaline and isoflurane he developed persistent hypercapnic respiratory failure with PaCO2 > 20. Conventional ventilation strategies were ineffective with poor compliance, high peak airway pressures and prolonged inspiratory times resulting in air trapping and hyperinflation. Therefore an iLA was inserted on day 2. This resulted in enhanced CO2 removal (Pa CO2 21 down to 50ACO2 7.6) and allowed protective lung ventilation at lower pressures with less gas trapping and hyperinflation. The iLA was removed on day 12 with spontaneous breathing on day 19. This could represent a useful future strategy for persistent hypercapnic respiratory failure unresponsive to conventional measures in obstructive diseases such as asthma and COPD.

**P2041**

Inhalation of activated recombinant factor VII to treat pulmonary hemorrhage in a patient with cystic fibrosis

Constantin Marcu, Robert Bal, Andreas Groeschel, Christian Lench, Julia Woerner, Sebastian Faerndich. Pneumologie, Staatliche Universität Hospital, Homburg/Saar, Germany

**Case:** The patient (30y.o., female) was diagnosed with cystic fibrosis as child. Currently, she was hospitalized with fever and bilateral pulmonary infiltrates. She rapidly deteriorated to respiratory failure with the need of extracorporeal membrane oxygenation (ECMO).

Diffus pulmonary hemorrhage complicated the course on ECMO. After 2 days of unmitigating bleeding with respiratory failure we used rFVIIa as an intervention of last resort. The patient was treated with inhalation of 30 μg/kg rFVIIa in 5 mL saline volumetrically delivered via a jet-driven nebulizer, which was repeated after 24 hours. Hemorrhage was visualized bronchoscopically, and its resolution following the treatment was immediate and did not occur again.

**Discussion:** Factor VII initiates clot formation by its interaction with TF. The FVIIa-TF complex activates factor X. Activated factor X activates prothrombin to thrombin, which converts fibrinogen to fibrin. Tissue factor is expressed in the lung alveoli during inflammation and therefore pulmonary administration of human recombinant activated factor VIIa (rFVIIa) could be a rational treatment option.

Our report indicates the applicability of topical rFVIIa to control unremitting hemorrhage in a patient with cystic fibrosis. Currently, she was hospitalized with fever and bilateral pulmonary infiltrates. She rapidly deteriorated to respiratory failure with the need of extracorporeal membrane oxygenation (ECMO). Inhalation of activated recombinant factor VII to treat pulmonary hemorrhage in a patient with cystic fibrosis
systemic exposure. This could also reduce the risk of thrombotic complications reported with systemic administration of rFVIIa as well as clotting in the ECMO membrane.

**Conclusion:** Intrapulmonary administration of activated recombinant factor VIIa (rFVIIa) via a jet-driven nebulizer may be an option in pulmonary haemorrhage.

**P2042**

Enhanced expression of Robo4 ameliorates LPS-induced acute lung injury in mice

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Pulmonary Department, Fudan University, Shanghai, China

The loss of endothelial integrity which causes leak of fluid and proteins into tissues contributes to the disease and death associated with acute lung injury. Silt2/Robo4 (an endothelium-specific) signaling promotes vascular stability. The purpose of this study was to evaluate the effect of enhanced expression of Robo4 on LPS-induced acute lung injury. We constructed a recombinant adenoaviral vector expressing murine Robo4 (Ad.mRobo4) which were administered intranasally to BALB/c mice. Forty-eight hours later, all the mice were administered a single dose of LPS via i.p. injection to induce acute lung injury. A second cohort of mice was followed for survival for 7 days. Administration of Ad.m Robo4 increased the expression of Robo4 in lung tissue, as determined by reverse transcription-polymerase chain reaction, Western blot, and immunohistochemistry. Enhanced expression of Robo4 in lung suppressed the inflammatory reaction to LPS, attenuated the lung pathological changes, significantly reduced vascular permeability and edema in the lung determined by albumin in bronchoalveolar lavage fluid and also improved the survival of mice. Our results demonstrate a novel function manner for silt2/Robo4 signaling. Silt2/Robo4 pathway work formerly mainly considered as ligand-dependently, it has now to be considered as a ligand-independently and thus could be an attractive adjutant in the treatment of acute lung injury.

**P2043**

Expression of osteopontin in the lung tissue of acute lung injury rats and the influence of osteopontin on TNF-a and IL-10

Wenjun Wang, Xiaming Fan.

The Department of Respiratory Medicine, Affiliated Hospital of Louchou Medical College, Louchou, Shichuan, China

This work was supported by International cooperation and exchange program of Sichuan science and technology department (NO. 2009HH0032); Background: Pathogenesis of acute lung injury (ALI) has not been clarified fully, also we need to improve the prognosis of ALI.

**Aims:** To investigate the expression of osteopontin (OPN) in the lung tissue of ALI rats and the influence of OPN on the level of TNF-a and IL-10 in serum.

**Methods:** 56 SD rats were randomly divided into control group (24 rats), ALI group (24 rats) and intervention group (24 rats). 8 rats in each group were examined at 2, 4 and 8 h. ALI was induced by LPS injection via caudal vein in ALI and intervention groups, at the same time, rats in intervention group were also injected with anti-OPN antibody. Wet/Dry Weight (W/D). Pathological changes of the lung tissue and ALI score were detected. The level of TNF-a and IL-10 in serum and the expression of OPN in homogenate of lung tissue were detected.

**Results:** W/D, ALI score and the level of TNF-a in ALI group at 2, 4 and 8 h were higher than those in control group and intervention group at the same time point (p<0.01). The level of IL-10 in ALI group at 2, 4 and 8 h was higher than that in control group (p<0.01), but was lower than that in intervention group at the same time point (p<0.05). Compared with control group, the expression of OPN in ALI and intervention groups at 2, 4 and 8 h was higher (p<0.01).

**Conclusions:** The expression of OPN in lung tissue of ALI rats induced by LPS was increased, and OPN could aggravate lung injury, which might be related to up-regulating expression of TNF-a and down-regulating expression of IL-10.

**P2044**

The role of osteopontin in the pulmonary fibrosis caused by acute lung injury induced by lipopolysaccharide in rats

Wenjun Wang, Xiaming Fan.

The Department of Respiratory Medicine, Affiliated Hospital of Louchou Medical College, Louchou, Shichuan, China

This work was supported by International cooperation and exchange program of Sichuan science and technology department (NO. 2009HH0032); Background: In the later stage of acute lung injury (ALI), lung fibrosis is a common sequel. It results in damage of lung function. But we know little about its pathogenesis.

**Objective:** To investigate the role of osteopontin (OPN) in the pulmonary fibrosis caused by lipopolysaccharide (LPS)-induced ALI.

**Methods:** 120 rats were randomly divided into control group (n=40), ALI group (n=40) and intervention group (n=40). ALI was induced by intraperitoneal injection with LPS on day 0, 1 and 2 in ALI group. Also, the rats in intervention group were treated with Anti-OPN antibody by intraperitoneal injection after LPS injection. Then 10 rats in each group were randomly sacrificed on the 7th, 14th and 28th day. Histological examination and the expression of OPN in the lung tissue were determined. Hydroxyproline and the mRNA levels of type I and II collagen in the lung tissue were measured.

**Results:** Compared with control group, the expression of OPN in ALI group was remarkably higher on 7th, 14th and 28th day respectively (p<0.01). The extent of lung fibrosis, the expression of hydroxyproline and the levels of type I and II collagen mRNA in intervention group and ALI group were higher than those in control group on day 7, 14 and 28 respectively (p<0.01), but they were lower in intervention group than those in ALI group (p<0.01).

**Conclusions:** The expression of OPN in the lung tissue of pulmonary fibrosis caused by LPS-induced ALI in rats was increased. OPN could promote the development of lung fibrosis in ALI rats.

**P2045**

A prospective evaluation of different anthropometric height estimation formula

Solene Guinard1, Zoe Chiche 2, Jérome Martin1, Erwan L’Her2. 1Medical ICU, CHU, Brest, France; 2Emergency Department, CHU, Brest, France

It is now accepted that protective ventilation with low (8ml/kg of predictive body weight) tidal volume benefits to ARDS patients. To determine protective body weight, the gender and height of patients have to be known. However, in the ICU or in the ED, patients are often unable to provide their height and tape measurement is usually not valid. The purpose of this study is to evaluate different easy and reproducible anthropometric indicators, which could be correlated to the exact patients’ height.

Several indicators have been prospectively evaluated on 60 healthy volunteers and correlated to their real height. Height evaluation formula are based on different simple measurements correlation coefficient (r) was calculated by linear regression as compared to exact measured height.

**Results:** See table 1. Among 16 anthropometric different height estimation formula, ulna’s length and tibia’s length were best correlated with the real volunteers’ height.

**Discussion:** Several simple limb measurements can accurately predict exact patients’ height. These estimations need to be tested on ICU patients, in order to evaluate their bedside feasibility and usefulness.

**P2046**

“Normotension” on admission to the emergency department affects outcome of patients with acute cardiac pulmonary edema (ACPE)

Valentina Ross1, Chiara Traverso2, Federico Piffer2, Stefano Alberti3, Caterina Bonino1, Valter Monzani2, Antonio Vora1, Daniele Camisa1, Simona Fuscò1, Marco Barchetti, Federica Molinaro1, Giuseppina Petrelli1, Roberto Cournten2, Anna Fanzia Brambilla1, 1Respiratory Medicine Department, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy; 2Emergency Department, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy; 3Emergency Department, San Gerardo Hospital, Monza, Milan, Italy; 4Emergency Department, Humanitas Hospital, Milan, Italy; 5Emergency Department, Melegnano Hospital, Melegnano, Milan, Italy; 6Emergency Department, Fuerza Hospital, Fuerza, Italy; 7Emergency Department, Sassuolo Hospital, Sassuolo, Italy; 8Emergency Department, Gradenigo Hospital, Turin, Italy; 9Emergency Department, San Benedetto del Tronto Hospital, San Benedetto del Tronto, Italy

**Introduction:** ACPE is a common cause of admission to the Emergency Department (ED). We previously retrospectively studied the effect on the outcome of blood pressure (BP) on admission.

**Aim:** To prospectively confirm the relationship between “normotension” on admission and worse outcome in ACPE patients.

**Methods:** Prospective, observational, multicentric, web-based study on patients admitted to the ED with ACPE. Data were collected from 13 Italian EDs. “Normotension” was defined as Mean Arterial BP (MAP)<107 mmHg. Patients with MAP>65 mmHg on admission were excluded.

**Results:** From May 2009 to October 2010, 460 patients were enrolled. Nine hypotensive patients were excluded. Mean age was 80 years (SD±10 years), 245 males (54%). “Normotensive” patients were 41% (185/451). Clinical and laboratory data are showed in table 1. Overall, in-hospital mortality was 8% (34/451). In-hospital mortality in normotensive patients was significantly higher than in hypertensive patients, 12% (22/185) vs 4% (12/266) (p<0.01). We also found that the risk factor “normotension” maintained its statistical significance in a multivariable analysis when compared with the other significant risk factors (Age, PaO2/ Hemoglobin) detected in our population in the univariate analysis.

Table 1. Correlation between real height and anthropometric indicators (we have only coccillaged each limb’s best formula in this table enhance readability)

<table>
<thead>
<tr>
<th>Anthropometric indicators</th>
<th>Male and female</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID card</td>
<td>r=0.963</td>
</tr>
<tr>
<td>Hand length</td>
<td>r=0.794</td>
</tr>
<tr>
<td>3rd phalanx index length</td>
<td>r=0.730</td>
</tr>
<tr>
<td>Ulna length</td>
<td>r=0.830</td>
</tr>
<tr>
<td>Tibia length</td>
<td>r=0.850</td>
</tr>
<tr>
<td>Simplified Chumlea</td>
<td>r=0.867</td>
</tr>
<tr>
<td>Right foot length</td>
<td>r=0.804</td>
</tr>
</tbody>
</table>

Simplified Chumlea is a specific way to measure tibia’s length in supine position.
A metabonomic approach to prognostic evaluation of ALI by high-resolution nuclear magnetic resonance (HR NMR) spectroscopy

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Purpose: Metabonomics is a well-developed platform for studying systems biology and clinical diagnosis. In this study, we investigated a metabonomic approach to prognostic evaluation of LPS-induced ALI by HR NMR spectroscopy.

Methods: The mice model of ALI was established by intratracheal instillation of LPS (5mg/kg) for 4 hours with the saline in control mice. The mice of dexamethasone (DEX) treatment group fell in the range of the control group.

Results: The lung injury score were significantly increased in ALI mice compared to control group and DEX treatment markedly decreased the lung injury score. The first principal component (PC1) shows a good separation between the ALI group and control (or DEX treatment) groups. The metabolites showed clear pattern recognition methods was applied to study 15 lung tissues extract samples of mice.

Conclusions: Our study, for the first time, provides evidence for a metabonomic approach to prognostic evaluation of ALI treated by DEX by HR NMR spectroscopy.

Conclusion: We prospectively confirmed that “nornotensin” on presentation is a significant and independent risk factor for mortality in patients with ACPE.

Materials and methods: This was a retrospective observational study of 366 patients with severe sepsis or septic shock who presented to the emergency department between May 2007 and July 2009. Compliance with resuscitation bundles and achievement of the corresponding end points were compared before and after the three-month educational program.

Results: Compliance with central line insertion and monitoring of central venous pressure (CVP) (29% vs. 67%, p < 0.001) and central venous oxygen saturation (ScvO2) (25% vs. 68%, p < 0.001) was significantly improved after the educational program. The achievement of target ScvO2 within the first six hours was significantly improved (62% vs. 88%, p < 0.001). In-hospital mortality was independently associated with adequate fluid challenge (OR, 0.161; 95% CI, 0.046 – 0.559) and the achievement of target mean arterial pressure (MAP) (OR 0.056; 95% CI, 0.008 – 0.384) and ScvO2 (OR, 0.231; 95% CI, 0.072 – 0.875) among the five sepsis resuscitation bundles.

Conclusion: An educational program can improve compliance with resuscitation bundles and achievement of their corresponding end points.

P2049
Prevalence and prognosis of critically ill patients with COPD between 1998 and 2008

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Background: Little is known about the prevalence and outcome of patients with COPD treated in ICUs. Such information is valuable for the planning of resources e.g. respiratory care units and weaning facilities.

Aims and objectives: We speculated that COPD would be an increasing problem in critically ill patients and would be associated with increased morbidity and mortality.

Methods: We analysed prospectively collected data of 194,453 adults treated in 87 Austrian ICUs over a period of 11 years (1998-2008).

Results: COPD was present in 9% of all ICU patients. The risk-adjusted mortality of patients with COPD was higher compared to patients without COPD (oberved to expected mortality ratio with 95% CI 0.91 (0.90 – 0.92) vs 1.14 (1.12 – 1.16), respectively). The presence of COPD was an independent risk factor for increased mortality in multivariable regression. Prolonged mechanical ventilation occurred more common in patients with COPD (24%) compared to those without it (17%), p<0.0001. Prolonged weaning was also more common in patients with COPD (6%) compared to those without (2%), p<0.0001. During the course of 11 years the incidence of acute respiratory failure due to COPD increased from 1.8% to 3.0%, p<0.0001) and the use of non-invasive ventilation more than doubled (from 15% to 34%, p<0.0001). Simultaneously, the risk-adjusted mortality of COPD patients improved.

Conclusions: Acute respiratory failure due to COPD is an increasingly common condition in critically ill patients. The presence of COPD is associated with increased morbidity and mortality. The improvement of risk-adjusted mortality over time may be attributable to the beneficial effects of non-invasive ventilation.

P2050
Acute and chronic term results of kyphoscoliotic patients with acute respiratory failure treated in intensive care unit (ICU)

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Objective: In our study we aimed to evaluate acute and chronic term results of kyphoscoliotic patients admitted to ICU with acute respiratory failure in 9 years period.

Method: Kyphoscoliotic patients applied to ICU between 2002-2010 enrolled in the study. Patients’ demographics,comorbidity,APACHE II score on admission, presence of sepsis, arterial blood gas analysis (on admission and first control), invasive (IMV) and noninvasive mechanical ventilation (NIV) application and duration, length of stay in ICU,ICU mortality, chronic term follow-up mortality were recorded. Data were summarized with descriptive analysis.Variables were given as median and interquartile ratio (IQR).

Results: 84 kyphoscoliotic patients (46 male) with median age 50 (IQR: 36-64) accepted to ICU were included: %78.3 (%57) of cases has comorbidity and 22.8% (%13.7) of patients were in long term oxygen therapy (LOT) and mechanical ventilation at home. APACHE II score 15 (12-19), presence of sepsis %42.9 (n=36), NIV and IMV application was %79.8 (n=67), %32.1 (n=27) respectively. Length of stay in ICU was 8 (4-14) days and mortality was %10.7 (n=9, 7 under IMV). After ICU discharge mechanical ventilator at home (HMV) was reported to %39.8 (%33) of patients, LOT was reported to %21.3 (%16) of patients. A total of 53 patients have HMV, 51 of these patients were followed long term. One patient after 2 months, 2 patients died after 5 years. 12 patients didnot come to controls regularly.
Conclusion: In patients with kyphoscoliosis accepted to ICU due to acute respiratory failure, mortality is significantly higher while in patients with mechanical ventilation at home compliance and follow-up is better, mortality is lower.

P2051 Characteristics and outcome of COPD patients with an acute exacerbation admitted to a respiratory ICU
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Many patients with an acute exacerbation may be considered for ICU admission. The aim of this study was to assess the clinical characteristics, resource use and prognosis of COPD patients in a respiratory ICU setting (RICU).

Methods: Retrospective study of RICU patients with primary diagnosis of COPD exacerbation from 1995-2007. We collected clinical information, ventilatory support requirements and outcome from the clinical records.

Results: During the study period 512 COPD patients were admitted with a mean age of 69.2±8.9 yr (86% male). Mean PEVI was 34.8±13.9 (% predicted value) and 40.4% were on long term home oxygen. More than half of the patients had one or more significant co-morbidities. Cardiac disease (26%) and alcoholism (14%) were among the most frequently encountered. As much as 49.4% of cases required intubation and mechanical ventilation (MV) while 38.9% could be managed with non-invasive ventilation (NIV). Only 5.8% of the patients treated with NIV at admission required finally MV. The duration of MV was 7.13 days (median 5.5, IQR Range: 3-9 days) and the overall ICU length of stay was 7.1 days (median 7.4, IQR Range: 2-8 days). Tracheostomy was performed in 4.7% of the cases. Finally, ICU mortality for all the study group was 9.4%. We did not find an association between mortality and PEVI or being on home oxygen therapy.

Conclusions: RICU mortality for COPD patients with acute exacerbation is lower than 10%. Most patients requiring MV could be extubated without major issues. A lower FEVI or being on home oxygen were not associated with a higher ICU mortality. COPD patients admitted to the ICU with an acute exacerbation have a good chance of survival.

P2052 COPD under invasive mechanical ventilation, in-hospital mortality rate: A retrospective study
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Background: The in-hospital mortality rate of patients with Chronic Obstructive Pulmonary Disease (COPD) submitted to Invasive Mechanical Ventilation (IMV) is recognized as being high.

The authors aim to characterize this population and to identify mortality predictive factors.

Methods: Retrospective study of the clinical records of 67 COPD patients admitted to the Respiratory Intensive Care Unit (ICU) of Lisbon-North Hospital required invasive ventilation between January 2005 and August 2009.

Results: The majority were male (91%), with an average of 69.1±10 yrs and 25% were active smokers. The FEVI was 40±18%, with 55% being subjected to Long Term Oxygen Therapy and 18% to domiciliary non-Invasive Ventilation (NIV). The aetiology of exacerbation was mostly infectious (78%). They required 16±7 days of IMV. The ICU mortality rate was 24% and the global hospital mortality rate was 40%.

Two groups were evaluated concerning mortality.

The statistically significant (p<0.05) prognostic factors were: older patients (75 vs. 66 yrs), lower BMI (24 vs. 26 kg/m²), pneumonia (40% vs. 15%), longer in-hospital period before ICU admission (8 v. 3 days), previous acute NIV (67% vs. 33%) and higher severity score at admission (SAPS II 44±23 vs. 35±17).

Conclusions: Mortality was associated to a higher severity at admission and extended period under NIV whilst preceding the admission in ICU. The data may be relevant through an early recognition of failure situations in patients with previous NIV.

P2053 pH – and serum sodium level as an important predictor of mortality in acute exacerbation of COPD
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Background: AECOPD result in increased morbidity and mortality, and constitute a tremendous socioeconomic burden. Predicting in-hospital mortality may aid prognostication and plan for future therapies.

Aim of study: Predicting in-hospital mortality in patient of Acute Exacerbation of COPD help in planning the course of future treatment for averting the impending morbidity and mortality.

Methods: Study includes 94 patients of Acute Exacerbation of COPD admitted in the Tertiary Care Hospital were subjected to thorough history and clinical examination, all relevant examinations including ABG & others like RFT, LFT, CBC, RBC etc were done. All the patients of AECOPD managed either by NIV or given invasive ventilation in ICU.

Results: Most patients were elderly with mean age of 62.3 years. Mortality rate was 17% (16/94) during hospital stay. Mean pH of the patients 7.382 (SD=0.0878). pH of those who survived were mean 7.3025 (SD 0.111) and patients who survived were mean 7.3898 (SD 0.706). The difference was significant (P=0.003) (CI 0.3385 – 0.15695). Sodium level of the patients in the study were 133.93 (SD 8.481), patients who expired the sodium level were mean 123.43 (SD 11.267) and those who survived mean sodium were 135.92 (SD 6.264). The difference was significant (P=0.001) (CI6.505 – 18.475).

Conclusion: pH and serum sodium level at the time of admission are independent predictors of mortality in patients with Acute Exacerbation of COPD.

P2054 Is there a difference in outcome according to etiology of COPD exacerbation in patients admitted to an ICU?
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Objective: the aim of our study was to detect the impact of the etiology of severe COPD exacerbations admitted to a respiratory intensive care unit (RICU).

Methods: Retrospective study evaluating all episodes of severe COPD exacerbations admitted from Jan/2005 to Sept/2010 in our RICU. Patients with lung cancer were excluded. Regarding the etiology of exacerbation we divided into three groups: heart failure, respiratory infection, others/undefined. Different parameters were analyzed: APACHE II, TISS, length of stay in RICU, days on invasive mechanical ventilation, mortality. In the comparative analysis, episodes with more than one cause of exacerbation were excluded.

Results: Data were collected from 141 out of 184 episodes admitted to RICU. Mean age was 70±10, 76% were male. Mean APACHEII was 24.6±7.9 and mortality during the RICU admission was 30%.

P2055 Intensive care resources and costs of advanced age patients with respiratory failure: 3 years cohort study
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Aim: Data about intensive care unit (ICU) stay days and costs of advanced age (>80) patients with respiratory failure is limited at our country. Aim of the study is to investigate ICU stay days and costs of advanced age patients. Method: Retrospective cohort study. Between 2008-2010, patients who were over 80 years old and stayed more than 24 hours at ICU were included. Patients' demographic characteristics, arterial blood gases, APACHE II scores, comorbidities, ICU and hospital stay days, mortality and costs were recorded from patients files. Patients were grouped according to Katz basic activities of daily living (ADL) scale as group 1 (0-6); independent, full function, group 2 (7-12) moderate impairment, group 3 (13-18) dependent, severe functional impairment. Results are recorded as median and interquartile ratio (IQR).

Results: 185 patients (109 women) whose median age was 82 (IQR, 81-84) were included. Patients ICU stay days were 6 (3-9), hospital days were 11 (6-17). Costs of ICU and hospital were respectively 1333.64 (693.18-2232.27), 1838.6 (983.58-2698.79) Euro. Groups according to Katz ADL scale: group 1: 159 (85.9%), group 2: 12 patients (6.5%), group 3: 14 patients (7.6). ICU costs (Euro) as follows; group 1: 1282.27 (595.00-2232.27), group 2: 1279.31 (758.40-2332.37), group 3: 1845.45 (1225.00-2232.27). ICU mortality was 16.6% but majority patients (80%) with group 1.

Conclusion: ICU survival of advanced age patients were nearly 80% and because
of comorbidities risk of ICU readmission is high. In order to decrease costs of these patients care especially bed dependent patients, government should developed health policy to build chronic care centers.

P2058

Factors affecting mortality in a respiratory intensive care unit

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Introduction and aim: Underlying diseases, comorbidities and hospital acquired infections are the main factors that affect mortality in intensive care unit (ICU) patients. In this study, the factors affecting mortality in respiratory ICU were evaluated.

Methods: The ICU patients followed-up between February 2008 and September 2010 were assessed retrospectively. The relationship between mortality and demographic features, underlying diseases, comorbidities, APACHE II and SAPS II scores on admission, invasive diagnostic and therapeutic procedures and, hospital acquired infections were investigated.

Results: Out of 240 patients (165 men, mean age 58.2±16.6 yrs) included in the study, 118 patients (49.2%) died. The mortality rate was higher in immunosuppressive patients than immunocompetent ones (71.4% vs. 41.2%, p<0.0001). The age, APACHE II and SAPS II scores were higher in patients who died (p<0.007, p<0.0001, p<0.0001, respectively). The mortality rate was 66.2% in patients treated with invasive mechanical ventilation (IMV), whereas it was 38.6% in patients using noninvasive mechanical ventilation (p=0.0001). The mortality rate was higher in patients with positive culture of respiratory samples on admission, 3rd and 7th days (p<0.05). Besides, the durations of intubation (p<0.0001) and ICU stay (p<0.020) were longer in patients who died.

Conclusion: Immunosuppression, severity of illness, IMV requirement and development of lower respiratory infections were the most important factors affecting ICU mortality.

P2059

The follow-up of cancer patients with acute respiratory failure in an intensive care unit


Aim: We intended to evaluate the follow up and mortality rate (MR) of cancer patients (CP) admitted to intensive care unit (ICU) with acute respiratory failure (ARF).

Material-method: Retrospective descriptive clinical study. Between January 2002- December 2010, all CP under medical treatment in ICU of Sureyyapasa Chest Diseases and Thoracic Surgery Teaching Hospital were included. CP were grouped under the following categories: underlying diseases, comorbidities and ICU admission priority.

The demographics, initial APACHE II score, application of noninvasive and invasive mechanical ventilation (NIV, IMV), length of stay (LOS), resectional surgery for lung cancer (LC) and tracheostomy, MR and distribution of cases according to years were investigated. Above data of mortal cases were compared with cases without mortality.

Results: Median age of 223 CP in ICU was 65 (57-71), 25%-75%: 81,8% (n=181) were male. Number of CP according to years in 2002, 2010 was 5 and 72, respectively. Rate of LC and resectable LC cases were 72.2% (n=161) and 29% (n=65), respectively. The median initial APACHE II and LOS in ICU were 21 (16-27; 25%-%75%) and 6 (3-12; 25%-%75%). Use of NIMV, IMV and tracheostomy were 63.7% (n=142), 48% (n=107), 3.1% (n=7), respectively. MR was 37.6% (n=84) for all CP. The MR for IMV and all CP were 63.7% (n=142) and 37.6% (n=84), respectively. APACHE II score and male gender were detected to be significantly high in mortal cases (p<0.001, p=0.043, respectively).

Conclusion: As MR of CP followed in ICU has declined, high APACHE II score and IMV need significantly increase mortality. We assume that MR for CP will decrease if proper therapy is chosen with NIV for CP at third or fourth level of ICU admission priority.

P2060

Intensive care outcomes in patients with diffuse fibrotic parenchymal lung diseases


Aim: We aimed to evaluate outcomes of patients with interstitial fibrosis (IF) and diffuse lung parenchymal diseases admitted to intensive care unit (ICU) due to acute respiratory failure (ARF).

Methods: We included patients with ARF due to IF and diffuse parenchymal lung diseases in ICU between 2008-2010 in retrospective cohort study. Patients demographics, APACHE II score on admission to the ICU, application of mechanical ventilation; invasive (IMV) or noninvasive (NIV), arterial blood gases values, type of feeding (oral, enteral, parenteral), length of stay (LOS) in ICU and mortality were recorded from patients' file. Continuous variables were given as median and interquartile range (IQR). Patients were compared according to mortality and logistic regression analysis was used for mortality risk factors.

Results: In study period 44 patients (26 male) and median age was 59 (IQR: 49-63), APACHE II score was 20 (13-32) and median of NIV and IMV were 20 (4-55.5), 17 (3-38.6) respectively. Oral, enteral and parenteral feeding as follow: 20 (4-55.5), 16 (3-36.4), 8 (16.18). LOS in ICU was 5 (2-9) days and mortality rate in ICU was 34.5 (n=20). Risk factors for mortality were found IMV application and enteral-parenteral feeding, p values Odds ratio (OR) and confidence interval%/95 (CI) respectively p< 0.036, OR:20.35 (CI:1.21-341.63), p= 0.020, and 45.63 (CI:1.67-362.32).

Conclusion: Patients with diffuse parenchymal lung diseases and IF have higher mortality in ICU if conditions with ARF prevent oral nutrition and there is need for continuous mechanical ventilation. Physicians should think carefully about ICU demand for those patients.
P2061
Health-related quality of life after automated or protocol-based weaning from mechanical ventilation
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Introduction: Although automated weaning systems have shown to be safe and more efficient than a conventional approach, it is unknown whether they influence health-related quality of life (HRQOL).

Objective: We hypothesized that automated weaning with SmartCare/PS compared with a standardized weaning protocol has a positive effect on HRQOL.

Methods: Patients were systematically followed-up one year after participation in a randomized controlled trial investigating the effect of automated versus protocol-driven weaning from mechanical ventilation (ASOPTrial; clinicaltrials.gov ID 00445289). Quality of life was assessed using QLQ C-30 3.0 questionnaire. Mean differences of equal or more than 10 score points were considered to be clinically relevant.

Results: 300 patients were initially included, 232 patients were alive one year later. We were able to get into contact with 143 patients, 127 patients gave consent to fill out the questionnaire. 81 questionnaires were sent back and included into this analysis. Regarding the function-related scales we found clinically significant higher mean score values for “emotion” and “global health status” in the automated weaning group (Figure 1, Panel A). Symptom-related scales like “fatigue” and “diarrhoea” were clinically significant lower in the SmartCare/PS-group (Figure 1, Panel B).

Conclusions: This study shows an improved HRQOL in the automated weaning group.

P2062
Validation of the 3CPO-score in a prospective cohort of acute cardiogenic pulmonary edema (ACPE) patients
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Introduction: Assessing the severity of patients presenting in the Emergency Department (ED) with ACPE is crucial to decide intensity of treatment and site of care. The 3CPO Trialists elaborated a Score based on presenting characteristic to predict 7-day mortality.

Aim: To validate the 3CPO-score in a prospective cohort of ACPE patients.

Methods: A multicentric, prospective, web-based, observational study was performed in 13 Italian ED. The 3CPO score was computed as follows: 0 to 2 points according to age; 0 to 3 points according to Systolic Blood pressure; 0 to 2 points according to the ability to obey to commands.

Results: From May 2009 to October 2010, 240 patients were analyzed. Mean age was 80 years (SD±11 years), 117 male (48%). Overall 7-day mortality was 7% (17/240). Mortality according to the Score classes is shown in table 1. The result of the ROC analysis is depicted in Figure 1: the AUC was 0.75; however, intermediate values of the score did not reliability predict mortality in our population.

Rationale: Nosocomial pneumonia (NP) is the most important infection acquired in ICU. There is no clear and validated definition to evaluate treatment failure (TF).

Objective: To validate a previously established definition of TF of NP in ICU.

Methods: We prospectively collected data of NP in ICU, evaluated the rate of TF at 72 hours after beginning antibiotic treatment and compared the groups with or without TF. TF was defined as the presence of any of the following: failure to improve the PaO2/FiO2 ratio or need for intubation because of pneumonia, persistence of fever or hypothermia plus purulent respiratory secretions, worsening of the pulmonary infiltrate by >50%, or occurrence of septic shock or multiple organ dysfunction not present on day 1.

Results: We evaluated 297 cases; 178 with ventilator-associated pneumonia (VAP) and 119 with non-VAP. 165 patients (55%) fulfilled TF criteria. There was no difference between groups in demographics, severity scores (APACHE-II, SOFA), or inflammatory response assessed by CRP (TF vs. non-TF). Treatment failure was related with increased mortality in the ICU (45% vs. 18%, p<0.001) and the hospital (52% vs. 25%, p<0.001), longer ICU stay (22±22 vs. 16±21 days, p<0.033), but with similar hospital stay. Failure to improve the PaO2/FiO2 was the only independent component of TF definition associated with the evaluated clinical outcomes.

Conclusion: The definition of TF appears to correlate well with relevant clinical outcomes, mainly due to the respiratory parameters.

P2064
Reversibility of swallowing disfunction in tracheotomized patients
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Fondazione Maugeri, Monza, Italy Neurological Rehabilitation, Fondazione Maugeri, Pavia, Italy Radiology, Fondazione Maugeri, Pavia, Italy Biometry and Statistics, Fondazione Maugeri, Pavia, Italy Respiratory Medicine, Ospedale Sant’Orsola, Bologna, Italy

Tracheotomized patients (TP) are often dysphagic and videofluoroscopy (VF) represents the gold standard diagnostic technique. We wanted to evaluate with VF the swallowing function (SF) of a group of 80 TP admitted to our centre: 48 (group N) were free from a chronic respiratory disease (CRD) and had been tracheotomized for a central nervous system hemorrhage or ischemia while the other 32 had been tracheotomized for the exacerbation of a CRD (group P). All patients were studied
with VF twice: few days after admission (t0) and after the rehabilitation period (t1). The following aspects of SF were assessed: glottis elevation (E), epiglottis folding (EF), oral phase (OP), pharyngeal retention (PR), onset of reflex (OR), penetration (P) and inhalation (I). Every item was scored 1, 2 or 3 when it was judged, respectively, normal, slightly altered or abnormal. Differences in terms of categorical scores distributions between the two groups were tested with Pearson’s chi square test, while t0 and t1 scores were compared separately for each group by Wilcoxon test to search for an improvement. At t0, Tp in group N exhibited better scores than Tp in group P with respect to EF, PR, P and I (p<0.02). At t1, Tp in group P significantly improved their scores compared to t0 with respect to AE, EF, OP, PR, P and I (p<0.02), while Tp in group P improved only for I (p<0.01).

In conclusion, the presence of a CRD significantly impairs the SF, mainly for the disrupted coordination between swallowing and breathing. Even at the end of a rehabilitation course, Tp affected by a CRD exhibit limited improvement, while those suffering from previous cerebral ischemia or hemorrhage significantly improve their SF.

250. Noninvasive ventilation in the acute setting: education, organisation, H1N1, paediatrics, weaning, diagnostic procedures and special considerations

P2065 A five-year series on the use of noninvasive ventilation as a weaning tool from invasive ventilation
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Data from randomised-controlled trials suggest that use of noninvasive ventilation (NIV) as a weaning tool decreases mortality, length of stay (LOS) and duration of invasive ventilation. We aimed to evaluate if increased use of NIV after high-risk extubation over time was associated with improvement in outcomes in the clinical setting.

In this prospective cohort study of all invasively ventilated patients (n=2316) in our medical intensive care unit (ICU) between 2006-2010, we performed time-trend analyses using simple logistic and linear regression to determine temporal changes in post-extubation NIV use, ventilator days, ICU LOS, reintubation rates, and ICU mortality. During this time we had gradually implemented the use of NIV post-extubation in patients with risk factors for extubation failure.

The proportion of patients receiving NIV post-extubation increased from 2006-2010: 21.1%, 22.0%, 23.9%, 34.6% and 34.8% respectively (OR 1.20 with each year passing, 95% CI 1.12-1.29). The commonest indication for NIV was high-risk extubation despite a successful spontaneous breathing trial (79.1%). Increased NIV use was associated with temporal decreases in invasive ventilator days and ICU LOS but these were neither statistically nor clinically significant. There were significant associated decreases in overall reintubation rates (OR 0.87 per year, 95% CI 0.76-0.99) and ICU mortality (OR 0.82 per year, 95% CI 0.76-0.87).

Although greater use of NIV post-extubation did not reduce ventilator days and ICU LOS in a general medical ICU population, there were associated improvements in reintubation rates and mortality. Considerations included a heterogeneous population and sedation protocols.

P2066 Techniques of managing difficult to wean acute NIV: Comparison between prolongation of time off ventilator and pressure withdrawal
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Introduction: Recent guidelines suggested gradual reduction of the duration of NIV once clinical improvement is determined. However, a subgroup of patients become dependent on the machine, finding the hours off the machine stressful in the absence of signs of respiratory failure. In this particular group of patients, we compared between slowly prolonging the hours off ventilator as tolerated by the patient to starting Day 0 and reducing the IPAP levels by 1-2 cm H2O every day.

Methods: Difficult to wean patients were identified as those unable to tolerate more than one hour off BiPAP on day 3 from the start of NIV. We excluded patients with persistent severe abnormal physiological parameters. All patients were fully alert with no clinical signs of persistent exacerbation. The failure of tolerating more than one hour off ventilator was due to the subjective feeling of tiredness and breathlessness in the absence of desaturation. Five patients (Group 1) were started on Day 0 and gradually reducing the IPAP levels by a rate of 1-2 cm H2O per day depending on the Day 3 IPAP level. The other five patients (Group 2) were treated in the conventional way of gradually prolonging time off ventilator as tolerated by the patient. Both groups received same medical management, phystherapy and psychological support as needed.

Results: Both groups did not differ significantly in age, sex, physiological parameters or blood gas values. The length of NIV therapy and the length of stay in the hospital were significantly shorter in group 1.

Conclusion: Gradual reduction of IPAP level can be used as an alternative method in a specific group of difficult to wean NIV patients.

P2067 A new weaning and long term ventilation service – One year on
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Introduction: In 2010 a purpose built 10 bed ventilation Inpatient Centre (VIC) was opened. In its first year 230 patients received acute non invasive ventilation (NIV), and 164 early electively on domiciliary NIV. It now also manages weaning failure for tracheostomy ventilated ICU patients in a multidisciplinary, rehabilitation centred environment. The cost is less than half that of an ICU bed. A secondary role is assisting discharge of ventilator dependent patients to home or care facility. Well established in continental Europe and the USA, such units are rare in the United Kingdom. We reviewed our weaning cases to report our first year results.

Results: Completed patient episodes 2010-2011

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<th>n=11 (male: 5 female)</th>
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<tr>
<td>Median age (years)</td>
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LoS, length of stay.

Conclusion: Activity has risen steadily, all weaning beds are currently used with a waiting list for transfer. Most patients had an underlying diagnosis likely to prevent complete liberation from ventilatory support. Success in weaning from invasive ventilation has been largely through the use of nocturnal NIV. The service has been well received by patients, families and referring ICUs. ICU beds can be used for acute care, it is cost effective and provides a template for other service development.

P2068 Noninvasive positive pressure ventilation in burn patients
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Introduction: Acute respiratory failure is a common complication of severely burn-injured patient. Noninvasive Positive Pressure Ventilation (NIPPV) has been used with success in hypercapnic and hypoxaemic acute respiratory failure. However, the outcome of NIPPV with burn patients is less well documented.

Objective: The purpose of this study is to report our experience with NIPPV in a series of burn-injured patients.

Method: The records of all burn patients from July 2008- January 2010, in whom NIPPV was used at the Intensive Burn Care Unit, were reviewed. The criteria for selecting patients for NIPPV included a combination of the following factors: patients with acute respiratory failure, haemodynamically stable, conscious and cooperative with their treatment. There had to be no need for endotracheal intubation.

Results: Thirty five patients were treated with NIPPV. Twenty were female. Mean age was 49.8 years, mean total body surface area (TBSA) was 37.63%. NIPPV was used to treat hypoxia in 24 patients, hypercapnia in 4 patients and both of them in 7 patients. NIPPV was used to treat acute lung injury in 15 patients, pneumonia in 9 patients, atelectasis in 6 and cardiogenic oedema in 5 patients. Mean PaO2/FiO2 ratio...
before NIPPV was 177 and after NIPPV was 304. Intubation was successfully avoided in 16 out of the 35 (45.7%) patients. All of these patients progressed to self-ventilation status following NIPPV.

**Conclusion:** The use of NIPPV with burn-injured patients is, as yet, unclear because of little work has been documented. In our experience, the use of NIPPV can lead to the need for endotracheal intubation and mechanical ventilation.

**P2069**

Efficacy of noninvasive positive pressure ventilation during fiberoptic bronchoscopy: Bi-level vs CPAP valve

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**Background:** Fiberoptic bronchoscopy (FOB) in severe acute respiratory failure patients may have risks and sometimes is contraindicated. Noninvasive Positive Pressure Ventilation (NIV) application to assist spontaneous breathing during FOB can be an alternative.

**Objective:** Compare the application of NIPPV (Philips-Respironics BiPAP Vision and Airon Supportor) vs Continuous Positive Airway Pressure (CPAP) valve (Boussignac) (CV) during FOB, in hypoxic and/or hypercapnic patients, with various etiologies.

**Patients and methods:** Fifteen (5 female) with severe hypoxemia defined by PaO2/FiO2 <200 and PaCO2> 60mmHg, submitted to FOB were eligible to the study. Seven patients were randomized to NPPV group (G1) and 8 to CV group (G2).

**Results:** At baseline 2 patients (G1) and 1 patient (G2) had PaCO2> 45mmHg.

**Conclusion:** This results suggest that noninvasive positive pressure has an important role as adjunctive technique during FOB in severe hypoxic patients (PaO2/FiO2<200). In this preliminary study no advantage of NIPPV vs CV.

**P2070**

NIV for ventilatory support during percutaneous endoscopic gastrostomy (PEG) in ALS patients with respiratory failure

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**Aim:** The aim of the study is to evaluate safety and usefulness of PEG placement in ALS patients with respiratory failure supported with NIV during this procedure.

**Material and methods:** We analyzed the group of 17 ALS patients with respiratory failure admitted for PEG placement and starting NIV on period of two years (2007-2009).

**Conclusion:** In ALS group (91±0.54kPa). Mean FVC was 38±15.01%. Bulbar symptoms had 11,06 (10 males and 7 females).

**Results:** 21 patients were identified. All patients had a restrictive pattern in lung function tests (VC 50 ±9% predicted). Sniff nasal inspiratory pressure was decreased (29±4 cmH2O), daytime blood gases showed hypercapnia in the majority of patients (mean daytime PaCO2 6.5±0.6 kPa). PEG was performed by two experienced gastroenterologists using the “pull through method”. Oxygen was delivered with a target saturation of 92%. Conscious sedation was reached by bolus administration of propofol. PEG placement could be performed successfully in all patients. Adverse events requiring noninvasive or invasive ventilation were not observed.

**Conclusion:** PEG placement under propofol sedation in patients with ALS is safe and acute respiratory complications are rare. Compared with controls the decrease of oxygen saturation during the procedure is lower. This is probably due to a more cautious dosing of propofol.

**P2072**

Noninvasive ventilation (NIV) after lung resection (LR) to prevent respiratory complications (RCs) in COPD patients (pts) (POPVNI trial)

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**Background:** RCs are common following LR in COPD pts. NIV decreases the rates of tracheal intubation and mortality in post-operative (PO) acute respiratory failure. The aim of our study is to prophylactic NIV for prevention of RCs in the immediate PO care of pts with COPD.

**Patients and methods:** This multicenter, prospective, randomised, parallel, open ended study planned to enrol 360 pts with moderate to severe COPD scheduled for LR. Patients were randomized to standard treatment without or with NIV during the first 3 PO days. The primary outcome is the incidence of acute respiratory events (AREs), defined as the occurrence of at least two of the following: RR >30/min, PaO2/FiO2 ≤200 mmHg, > 10 mmHg increase in PaCO2 or a new pulmonary infiltrate on chest X Ray: Secondary outcomes are the incidence of RCs, rescue NIV use, invasive ventilation requirements, mortality rate, duration of ICU and hospital stay. Univariate and multivariate analysis will identify subgroups who benefit more from NIV.

**Results:** 351 pts, 277 men (79%) and 74 women (21%) were effectively included in 6 centres between June 2008 and October 2010. Mean age (±SD) is 62±9 years. Mean pre-operative FEV1 is 62±11% predicted. Pts numbers in GOLD stage II, III and IV are 295 (83.4%), 44 (12.5%) and 4 (1.1%), respectively. There is no difference in baseline patients’ characteristics at inclusion between the control group (n = 174) and NIV group (n = 177).

**Conclusion:** Comparability of the 2 groups at baseline will allow reliable comparisons of outcomes (which will be available at the ERS meeting) between PO NIV and standard care following LR in GOLD stage II-III COPD patients.

**P2073**

The provision of an acute paediatric NIV service at a district general hospital

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The experience of acute NIV in Paediatrics is limited. The experience outside a PICU is even more limited. We looked at our acute NIV usage over a 3 year period (January 2007 to December 2009) in a Paediatric HDU at a District General Hospital with no PICU facilities. The indication for NIV was Type 2 respiratory failure as defined by pH <7.30, PaCO2 >60 mmHg.

**Conclusions:** The vast majority of children (Group 1) admitted with acute respiratory failure needed NIV; the largest diagnostic group was children with SMA followed by Duchenne muscular dystrophy. 10 children (Group 2) who were stable on NIV were admitted with a respiratory failure and needed increased NIV support. The largest diagnostic group in this cohort was children with Duchenne Muscular Dystrophy. 11 of the 14 children in group 1 and all 10 of the children in Group 2 improved clinically and on blood gases measurements were discharged home. NIV has been implemented successfully out with a PICU. There are significant benefits to the family and to the economy.

364s

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The use of non-invasive ventilation after liver transplantation in pediatric patients: Changes in the need for reintubation

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Introduction & aim: The role of non-invasive ventilation (NIV) in preventing reintubation after abdominal surgery in paediatric patients is uncertain and should be investigated.

Methods: Our team has performed more than 700 liver transplantsations (LT) for pediatric patients since 1990. Beginning in 2005 we began full introduction of NIV to these patients from 2005. We screened all medical records of pediatric patients less than 12 years old who underwent LT during two 4-year periods: 2001-2004 (pre full introduction of NIV) and 2006-2009 (post full introduction of NIV) and retrieved data on cases at high risk of respiratory failure. Data and clinical outcome for these cohorts were retrospectively analyzed and compared.

Results: In the analysis were included 54 cases (53 patients) from the pre-NIV period and 29 cases (28 patients) from the post-NIV period. After full introduction of NIV, NIV was applied more frequently within one week after extubation in these patients (16/25 cases (64.0) vs 24/29 cases (82.8), p<0.01) and the need for reintubation was significantly decreased (11/54 (20.4) vs. 1/29 (3.7%), p<0.05) during that period. Sequential arterial blood gas analysis suggested that NIV use beginning immediately after extubation stabilized the respiratory condition in this cohort.

Conclusion: NIV is an acceptable method of respiratory management of pediatric patients undergoing LT. NIV may also stabilize their respiratory function and decrease the need for reintubation after scheduled extubation.

Non-invasive ventilation in H1N1 acute respiratory failure in emergency department: A case series

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Background: The recent ERS/ESICM guidelines do not recommend the use of non-invasive ventilation (NIV) in patients with severe pneumonia caused by H1N1 infection.

Methods: We retrospectively reviewed the clinical data of 9 consecutive patients with severe respiratory failure due to H1N1 virus, admitted to the Emergency Department of Fondazione IRCCS Ca’ Granda Policlinico (Milan, Italy), between January 1 and February 20, 2011.

Results: Patients were predominantly male (66%), mean age was 55 years (range 34-79).379 patients had one or more risk factors for severe H1N1 infection: obesity, chronic pulmonary disease, onco-haematologic disease, age ≥65 years. All patients presented with high fever (>38°C), cough, dyspnea and multifocal bilateral consolidations on chest X ray. 69 patients developed ALL 29 patients presented with ARDS. All patients received oseltamir and empirical antibiotic therapy. 7/9 patients were immediately treated with NIV (6 CPAP, 1 BiLevel). 57 patients developed severe sepsis; no patients showed signs of septic shock or needed inotropic support. One patient needed endotracheal intubation. Only one patient died for acute respiratory failure due to nosocomial infection, all the others were discharged after a mean of 17 days (range 4-34 days).

Conclusions: NIV was successfully applied in the majority of patients (87%), and only one patient needed endotracheal intubation. Our data suggest that in particular settings with staff experienced with NIV, high monitoring level and rapid access to intubation and ICU, early NIV could be an option to improve oxygenation in acute respiratory failure due to Influenza A H1N1 infection.

The application of bi-level positive airway pressure in patients with severe pneumonia and acute respiratory failure caused by influenza A (H1N1) virus

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Objective: To evaluate the effect of noninvasive Bi-level Positive Airway Pressure (BiPAP) ventilation on the severe influenza A virus associated with pneumonia and acute respiratory failure (ARF).

Methods: Based on conventional therapy via face mask using BiPAP ventilator positive airway pressure ventilation in the treatment of severe pneumonia caused by influenza A (H1N1) virus with acute respiratory failure (ARF) in 18 cases, we observed and evaluated the therapeutic effects. Results: PaO2 and SaO2 before and after treatment were (48±5.0 vs.12.5±15.0mmHg, (68±6.6 vs.12.5±15.0) mmHg and (80±6.6), (92±5), respectively. The results were significantly different (P<0.05) before and after treatment. Endotracheal intubation rate was 25% (6/24) and case-fatality rate was 8.3% (2/24).

Conclusion: BiPAP ventilator airway pressure by face mask ventilation can reduce the rate of endotracheal intubation in the treatment of severe pneumonia caused by influenza A (H1N1) virus in acute respiratory failure. It could be an effective approach in the emergency treatment with clinical value.
P2079
Can repeated educational interaction improve doctors' knowledge of NIV management? 
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Introduction: Exacerbations of chronic obstructive pulmonary disease (COPD) requiring non-invasive ventilation (NIV) are common and often poorly managed [1]. Amongst other aspects, doctors on call in Southport may be asked for advice in adjusting settings appropriately.

Methods: On the background of a 6-12 monthly rolling teaching program a new educational intervention on NIV was established. Doctors of all grades completed a questionnaire containing 3 questions prior to receiving a presentation about NIV. The teaching was then repeated 3 months later and the same questionnaire completed afterwards. 3 clinical vignettes asked for the best change in settings in response to common scenarios (including intensive care, low PaO2, persistent acidemia).

Results: 21 questionnaires were collected before the first teaching session and 16 after the second. The table below shows the number of correct responses for each question.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>1st Questionnaire</th>
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<tr>
<td>1. 9/21 = 42.9%</td>
<td>11/16 = 68.75</td>
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<td>0.1845</td>
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<tr>
<td>2. 6/21 = 28.6%</td>
<td>11/16 = 68.75</td>
<td></td>
<td>0.0220*</td>
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<tr>
<td>3. 7/21 = 33.3%</td>
<td>6/16 = 37.5%</td>
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*Statistically significant (Fisher's test).

Conclusion: The survey shows that there is a lack of knowledge in important aspects of NIV. After an educational intervention some improvement was observed. We therefore conclude that an educational intervention such as ours combined with ward-based practical sessions is likely to be the best ways to improve standards of care. Frequency and intensity need further exploration.

References:

P2080
Effect of a structured education programme on the documentation of “ceiling of care” for patients with acute hypercapnic respiratory failure (AHRF) requiring invasive ventilation (NIV) 
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Introduction: With greater use of ward-based NIV, early documentation of decisions regarding ceiling of care of these patients is assuming greater importance. Nava et al. [1] showed that ceiling of care documentation was low in this group of patients. We conducted a survey of documentation of “ceiling of care” at our 11-bedded ward-based NIV unit in Birmingham, UK, providing acute medical services to a population of over 450000 to assess the effect of a targeted rolling education programme for the caregivers and the use of a standardised protocol.

Methods: Retrospective case note analysis of all patients commenced on acute NIV for AHRF between 1st January 2009 and 31st January 2010. Data relating to documentation of ceiling of care for patients, NIV outcome and mortality were collected after the educational intervention to improve practice.

Results: Over the 13 month period of data collection there were 264 NIV episodes for AHRF. Ceiling of care was documented in 165 patients (62.5%). NIV treatment failure occurred in 59/264 (22%). Eleven of 264 patients (4%) were admitted to ICU during this admission episode. The overall in-hospital mortality for the entire group was 12.8%.

Conclusions: Documentation of ceiling of care in NIV patients can significantly improve with the increase in awareness among caregivers following the introduction of a rolling education programme and the use of a standard protocol.

Reference:

P2081
Non-invasive ventilation (NIV) practices in Swiss adult ICUs 
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Purpose: The real scenario of the practical modalities for NIV in adult Swiss ICUs has never been reported.

Methods: Using the survey methodology, we developed a questionnaire addressed by e-mail to all directors of the 79 certified adult Swiss ICUs. Responses were analyzed using descriptive and standard statistics.

Results: We obtained replies from 49 of the 79 ICUs (62%). The overall Swiss utilization rate for NIV was 26% of all mechanical ventilations, but we found significant differences in the perceived utilization rates among different linguistic areas, from 20% in the German part to 48% in the French part (p < 0.01). NIV was mainly indicated for the acute exacerbations of COPD (AcOPD), acute cardiogenic pulmonary edema (ACPE), acute respiratory failure (ARF) in selected do-not-intubate patients and post-operative states, post-extubation failure in high risk patients and pneumonia in the immunocompromised host. CPAP use in ACPE was much less used than bi-level ventilation and was still applied in AcCPAP. The most important arguments reported by doctors perceiving low degree of satisfaction in the NIV application, were lack of medical technical knowledge and inadequate staff training.

Conclusions: This survey demonstrates that the perceived NIV practice is high in Switzerland, with significant regional variations. The indications of the perceived NIV use are in accordance with the institutional guidelines, but a high percentage of units considers selected do-not-intubate conditions an important indication for NIV. The variability of NIV application and some erroneous applications suggest that education and training of physicians, nurses and therapists are warranted.

P2082
Non-invasive ventilation as ceiling of ventilatory care (NIVc) in a respiratory intermediate care unit (RICU) 
Ana Soña Oliveira, Sara Salgado, Cecilia Nunes, Fernanda Oliveira, Cristina Bárbbara. Pneumology, Pdulo Valente Hospital, Lisboa, Portugal

Aims: In European RICUs an end-of-life decision is taken for 2.8% of the patients admitted. One of the most common practices is the use of NIVc. We aimed to characterize this group of patients under NIVc practice.

Methods: A systematic retrospective review of the patients admitted in our RICU for NIV, in whom an end-of-life decision was made, was carried between February 1 and July 31, 2010.

Results: Of the 126 admissions, 23 had an end-of-life decision (18%), in 10 decision was made pre-admission and in 13 during hospitalization. NIVc was initiated in 18 patients (78%), with a mean age of 74 yrs. (52-93) and 72% males. Patients were referred mainly from the Emergency Department (39%), Respiratory wards (22%) and other hospital wards (11%). All patients had chronic diseases, a quarter had neoplastic disease and diabetes, 77% pulmonary chronic disease, mostly severe, 89% cardiovascular disease, 17% neurologic disease, 50% renal insufficiency, 72% were on dialysis and 61% had previous hospitalizations in the last year. The majority had uncomplicated chronic diseases (83%) at admission (mainly pulmonary). The main diagnosis of hospitalization was pneumonia: the main cause for admission (56%). RICU mean stay was 9 days (2-23) and mean hospital stay was 19 days (2-71). At RICU admission, blood gases showed respiratory acidosis in 61%, hypoxemia in 22% and mixed acidoses in 17%. NIVc had success in 1 patient and 17 died (94%).

Conclusions: NIVc is used as an effective alternative in intubation in patients who have no invasive approach is questioned or as palliative approach. The high mortality found in our group of patients was related to NIVc on the end stage disease.

P2083
Respiratory intermediate care unit (RICU) – What are we doing? 
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Aims: RICUs are designed to treat invasive mechanical ventilated (IMV) stable patients for weaning and chronic care, hemodynamically stable patients with compromised gas exchange for frequent observation and/or non-invasive ventilation (NIV) and patients who require frequent vital signs monitoring or aggressive pulmonary physiotherapy. We aimed to evaluate the work developed in our RICU.

Methods: A systematic retrospective review was made from February 1 to July 31, 2010, in an 8 beds RICU.

Results: In the studied period, 105 patients were responsible for 126 admissions, 73% were male, mean age was 68 yrs. (16-96). Patients were referred mainly from the Emergency Department (44%), Intensive Care Unit (ICI) (21%) and Respiratory wards (11%). The reasons for admission were in 21% to step-down ICU, 52% for NIV, 24% for cardiopulmonary monitoring and 3% for other reasons. In 98% respiratory insufficiency was present, mainly hypercapnia, mostly caused by infectious respiratory exacerbations. All but 1 had chronic disease, 76% cardiac and 60% pulmonary (mostly severe). The average stay at RICU was 22 days (1-76). RICU had to liberate 536 days of ICU. Eleven patients were transferred to ICU and 20 died. One of them was weaned from chronic IMV. Tracheotomy was closed in 3 of 5 patients. In respiratory failure patients, NIV survived in 46 (70%), 4 were transferred to ICU and 16 patients under palliative NIV died.

Conclusions: Despite the diversity of work developed in our RICU, primarily it allowed free days in ICU and NIV practice. Although the advanced stage of chronic diseases and a high number of do not intubate patients, the possibility of close monitoring and observation is greatly possible in NIVc's success.
The introduction of a respiratory high care unit in a district general hospital

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Introduction: Non-invasive ventilation (NIV) has a well documented place in the management of the type two respiratory failure of COPD. Ward based NIV is cost effective when compared to administering the treatment in an Intensive Care Unit (ICU) setting.

Prior to March 2010, type 2 respiratory failure requiring NIV at the Lister Hospital was managed in ICU, under anaesthetic care. In March 2010, a 4 bedded Respiratory High Care Unit (RHCU) was created to deliver NIV in a ward environment.

Aims: To look at usage of the RHCU in the management of type 2 respiratory failure and the outcomes of those receiving NIV.

Methods: Bed occupancy records were kept from the introduction of the RHCU. These were analysed from May 2010 to January 2011 in conjunction with medical records to establish diagnosis, length of stay and discharge destination.

Results: 40 patients received NIV over the nine months. 31 (77%) had underlying COPD, 1 sleep apnoea and the remainder; heart failure, pneumonia, interstitial lung disease and motor neurone disease. Length of stay varied from 1-46 days (mean 11.3, standard deviation 9.7).

In the 31 patients with COPD, 6 already had home NIV, 6 were referred for consideration of home NIV, and 14 (45%) discharged with no need for ongoing ventilation. 5 COPD patients did not survive the admission.

Conclusion: COPD was the predominant diagnosis in the 40 patients treated with NIV. The introduction of the RHCU allowed savings through the avoidance of an ICU admission and meant a trial of NIV could be used more readily as a ceiling of treatment in end stage COPD. Of note, no COPD patients were transferred from the RHCU to ICU, indicating appropriate selection of patients for ward based NIV.

251. New evidence in home mechanical ventilation

P2085

Hemodynamic effects of non-invasive ventilation in patients with obesity-hypoventilation syndrome

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Background: Although it was occasionally reported that pulmonary hypertension (PH) is more frequent in obesity-hypventilation syndrome (OHS) patients than in "pure" sleep apnoea syndrome (OAS) patients, little is known about the haemodynamic repercussion of this entity. The aim of this study was to describe the hemodynamic situation -assessed by echocardiography and six-minute walking test (6MWT)- of patients newly diagnosed with the most severe form of OHS and to evaluate the impact of non-invasive ventilation (NIV) on it.

Methods: We conducted a prospective, descriptive, single-center follow-up study. At baseline, patients underwent echocardiography, spirometry, static lung volumes measurement, 6MWT, overnight pulse-oximetry and polygraphic recording. We assessed changes in echocardiographic findings and 6MWT after 6 months of NIV implementation. Right ventricular overload (RVO) was defined by the presence of right ventricular (RV) dilatation, RV hypokinesis, paradoxical septal systolic motion on/and PH.

Results: A total of 30 subjects (20 women; mean age: 69±11 years) were included. The percentage of patients with RVO did not change significantly after NIV (from 43.3% to 41.6%; p = 0.24). Pulmonary arterial systolic pressure (PASP) for patients with RVO at diagnosis decreased significantly at 6 months (from 58±11 to 44±12 mmHg; p = 0.014) and the mean distance walked on the 6MWT increased from 350±110 to 426±18 m (p = 0.006) without significant changes in the body mass index.

Conclusions: PH is a frequent finding in patients with the most severe form of OHS. Treatment with NIV leads to a decrease in PASP and an increase in the distance covered during the 6MWT.

P2086

The effects of non-invasive bilevel positive airway pressure ventilation on insulin resistance in patients with obstructive sleep apnea

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Background: The effects of the noninvasive ventilation on insulin resistance in obstructive sleep apnea (OSA) patients has been elusive. Although there are a lot of trials concerning its effectiveness, data is still conflicting. There is a lack of studies dealing with the results of the bilevel positive airway pressure (BiPAP) therapy.

Materials and methods: Thirteen patients with type 2 diabetes and eighteen insulin resistance and newly diagnosed OSA (AHI>30) received BiPAP therapy. Patients were followed up for a mean period of 3.9 months (±1.5) and had a compliance >80%. The average body mass index (BMI) was 38.17 and the mean AHI - 51.95. Baseline tests - blood glucose, HOMA-index, immunoreactive insulin (IRI) and Impaired fasting glucose at the end of the study.

Results: Results are given as mean ± (SD). Blood glucose measurements did not change significantly in none of the groups - type 2 diabetes (5.5mmol/l ± 1.8 vs. 5.4mmol/l ± 2.01); insulin resistance (6.4mmol/l ± 1.16 vs. 6.0mmol/l ± 1.38). There was a more significant decrease of IRI and HOMA – index the insulin resistance group – (IRI-21.06±11.9vs. 14.46±10.11). (HOMA-index – 5.23±1.18 vs. 3.74±1.12). In comparison the group with type 2 diabetes showed a lesser effect of BiPAP therapy (IRI-26.06±11 vs. 22.5±10.09). (HOMA-index - 7.7±4.6vs.6.01±2.7). Body mass index and waist circumference remained unchanged.

Conclusions: BiPAP therapy reduced the insulin resistance in obese OSA patients. The effectiveness was better in patients with insulin resistance than those with already overt type 2 diabetes. HOMA - index seems to be the most sensitive marker for the effect of BiPAP therapy.

P2087

Prevalence of patient-ventilator asynchronies and effects on sleep quality in neuromuscular patients using long term non-invasive ventilation

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Background: There are few studies on the association between asynchronies and arousals in patients using long term noninvasive ventilation (NIV) and among them, only one has been performed on neuromuscular patients. Moreover, in the real life of home ventilated neuromuscular patients sleep fragmentation is probably far from being perfectly corrected.

Objective: The aim of this work was to investigate the prevalence of patient-ventilator asynchronies and their association with sleep quality in stable neuromuscular patients chronically ventilated after optimization of ventilator setting.

Methods: Eighteen patients were included in the study. Sleep was recorded during ventilator application using standard polysomnography. Physiologic tracings were scored for autotriggerings, patient-ventilator desynchronizations, prolonged inspirations (PI) and respiratory arousals.

Results: Most frequent asynchronies were autotriggerings and desynchronizations (83.3% and 77.7% of patients, median 1.11 (IQR 0.43-2.84) and 0.23 (IQR 0.12-1.00) respectively). Desynchronization was the asynchrony most frequently associated with arousal (median 73.61%, IQR 15.91-96.88) followed by autotriggering (median 66%, IQR 0.90-90). PI was not frequent and almost never associated with arousal (median 0 IQR 0-100). Asynchronies were significantly correlated with leaks (rs=0.49 p < 0.05).

Conclusion: Patient-ventilator asynchronies may still occur in neuromuscular patients receiving long term NIV and can contribute to sleep fragmentation. Monitoring of quality of ventilation should be included in long term programme of neuromuscular patients.

P2088

Evaluation of inspiratory rise time versus resistances of four home ventilators

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There is no consensus neither literature nor constructor to define inspiratory rise time (TIR) which is equally called "pressure ramp slope" or "pressurization rate". The purpose of this study was to evaluate on a test bench the TIR of four home ventilators, versus different resistances.

SMARTAIR ST (Airox), TRIOLOGY100 (Respironics), VIVO40 (Brea, GE) and VPAPII (Resmed) were tested in a bilevel pressure support mode. All TIR avail- able were tested. Simulations were performed on an ASL 5000 (Ingmar Medical, Pittsburgh, USA) which simulates normal and obstructive lung. TIR has been de- fined as the delay between return to EPAP (Expiratory Positive Airway Pressure) after begin of inspiratory effort and time where pressure reaches 90% of maximal pressure. For each setting versus resistance, value of TIR, and slope of "pressure flow" in curves in their linear segment were calculated. Only TIR of VPAPII and TRIOLOGY100 don’t vary according to resistances. How- ever, values measured are always above than specified, particularly TRIOLOGY 100. TIR measured for SMARTAIR ST and VIVO40 decrease when resistances in- crease. Pulmonary dynamics can explain this results. In order to control this TIR, four strategies are observed. Resmed uses a fixed pressure slope, whereas Brea set a fixed flow slope. SMARTAIR maintains a fixed pressure slope until a preset time (300ms), after which slope vary versus resistance. Lastly, curve’s TRIOLOGY
is an exponential. This ventilator seems to maintain a fixed time constant on the pressure curve. We prove that ventilators have different strategies to achieve targeted maximal tidal volume and I/E-ratio in patients with COPD.

Method: For detection of volume changes, frequency variations and I/E-ratios we used two classical invasive measurement devices (telemetric thoracic catheter). The signal was relayed to a polysomnography device. Flows from 20 lpm up to 50 lpm with small, medium and large nasal prongs were tested. To compare the results with a closed ventilation support system, the measurements were also performed with CPAP (6 and 10 mbar) and BiPAP (14/6mbar). We compared the results with values measured during spontaneous breathing.

Results: nHF led to a significant decrease in minute volume, tidal volume and breathing rate in healthy volunteers in comparison with spontaneous breathing. The I/E-ratio results in no significant changes. In patients with COPD the breathing rates were also decreased, but the tidal volumes were increased with partial reductions in minute ventilation. The I/E-ratio was not changed in COPD. In comparison with spontaneous breathing, CPAP and BiPAP showed significant changes in patients with COPD.

Discussion: nHF resulted in significant effects on respiratory parameters of healthy volunteers and in patients with COPD. The changes deliver a possible explanation of the active manner of the breath support and the decrease in PCO2.

P2090
Validation design for a method to determine respiratory resistance and compliance in non-selected patients
Krestel Lopez-Nivas, Hartmut Gehring, Ulrich Wenkelbuch. Laboratory of Medical Systems, University of Applied Sciences Luebeck, Luebeck, Germany

Advantageous ventilation modes like pressure support PS require the accurate setting of parameters based on individual characteristics of the patient's respiratory system. As these change, a method for their continuous measurement is necessary. We tested a novel method for the "Deltan+" method (Delta technique focused on expiratory occlusions) by estimating respiratory resistance R and compliance C using flow and pressure data gained from a software-controlled lung simulator programmed to represent four cases with increasing work of breathing and available real data from 6 volunteers and 6 patients. Using the delivered values the transdiaphragmatic pressure (Pdi) was reconstructed as repre-sentation of muscular effort.

The measured Pdi and its reconstruction were compared using the inspiratory Pressure Time Product (PTPinsp). The correlation from simulated data was high (R2 =0.90a,0.05) permitting to validate the relevant analysis systems, but the correlation from real data was low (under 0.68) which was associated to difficulties at measuring Pdi without artifacts and compliance unwantedly attached to the system. We present now a test setup and methodology to investigate real data more accurately. This includes measurement of flow, airway- and transdiaphragmatic pressure from volunteers with minimized susceptibility to artifacts, improved control of mechanical problems and higher sampling rate. The integration of hardware required for occlusion to the ventilator and experienced measurement of Fdi intend to increase the number of parameters determining parameters using software for improved recognition of outiers including online analysis.

P2091
Adaptation of children with spinal muscular atrophy type 1 and 2 to non invasive ventilatory support
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Spinal Muscular Atrophy (SMA), the most common fatal inherited disease in infants. The impaired respiratory function is the main cause of the high mortality. Non Invasive Ventilation (NIV) has reduced morbidity and mortality due to respiratory insufficiency and has a favourable impact on respiratory infectious complications.

Aim: Evaluation of the necessary time and mode to achieve adaptation to this tool in SMA patients (pts) free from acute respiratory insufficiency. We prospectively studied 28 consecutive SMA type 1 pts (11 pts) and 2 (17 pts), who were enrolled in a standardized clinical protocol of adaptation to NIV. Mean age was 19±23 months, M/F 10/18. NIV was delivered via a nasal mask in 23 pts, nasal prongs in 4 pts, full face mask in one, with Pressure Support Ventilation (PSV) mode (25 pts) and Assisted Controlled Pressure Ventilation (ACPV) mode (3 pts). Mean IAP was 12±2.7 cm H2O, mean EAP 9±6±74 cm H2O. Success was defined as the necessary time to accustomed the SMA pts free from acute respiratory insufficiency to NIV and the mode to achieve acceptability of this tool.

According to this definition, all pts (100%) were considered as successfully ventilated, as all of them tolerated NIV with a mean adaptation time of 8±2 days. No major complications were observed.

In conclusion, our study demonstrates that NIV is well tolerated in SMA children and, probably, the high rate of success was obtained thanks to a standardized protocol of NIV initiation/administration, the proper parents education, a strict follow-up, the lack of major complications. With these assumptions, success can be expected in a high rate of pts before the onset of respiratory insufficiency.
Introduction: Home high-flow therapy is another option of respiratory support in sleep and ventilation medicine. But the precise pathophysiological effects (reduction of dead space ventilation, development of a PEEP) remain unknown, and the patient group, that may profit of such therapy, is not defined.

Question: Compared are respiratory frequency (RF) and gas exchange under nasal high flow therapy of 20l/min (applied through one and both nares of the nose) with the effect oxygen therapy (LOT) of 2 l/min at 21 patients with stable hypercapnia in a prospective randomised order for always 45 minutes while awake.

A capillary blood gas analysis (BGA) was made after each phase, as well as a 15 minutes break.

Results: The mean RF/min was under LOT 19.4±4.0 and was reduced to 17.8±4.7 under double sided TNI application and 17.7±4.3 under single sided TNI application (difference between LOT and single sided: p=0.043).

Methods: A cross sectional study was performed in patients with COPD treated by home NIV. The aim of the study was to determine predictive factors for COPD failure. The clinical baseline data of patients treated with home NIV were collected. Survival of home NIV patients was analyzed by Kaplan Meier survival analysis and receiver operating characteristic (ROC) curve was performed to determine the variables for successful home NIV treatment. A principal component having an area under the curve (AUC) more than 0.7 was suggested predictive.

Results: NIV was successful in 68% of patients. We found principal component capturing the baseline FVC and FEV1, to be the best predictive variable for failure of treatment (AUC=0.9, sensitivity 90%, specificity 80%), however the other covariates were less useful.

Conclusion: Baseline lung function may be helpful to predict which patient is susceptible to receive additional endotracheal intubation.
Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease which usually leads to respiratory failure, requiring Noninvasive Ventilation (NIV) or tracheostomy. No data exist on predictor factors of tracheostomy at the clinical onset of disease.

A retrospective study was designed, in a population of 71 consecutive ALS patients (39 males), to evaluate anthropometric, clinical, and functional indicators of the need of tracheostomy, including age, sex, BMI, site of onset, time of diagnosis, co-morbidities, tobacco habit, traumas, sport activity, and sleep disorders breathing markers. Arterial Blood Gas analysis and respiratory functional test, including FVC, FEV1, as well as Sniff Nasal Inspiratory Pressure (SNIP) were also measured at first ambulatory control.

We found that SNIP test, at first control, positively correlated to the need of tracheostomy (p<0.001) in the entire population observed. The mean SNIP test value of the group who was admitted to tracheostomy was 25.12 ±25.25 compared to a mean SNIP value of 54 (25.46) in the group who did not undergo tracheostomy. Other anthropometric, clinical, functional, and nocturnal parameters evaluated did not correlate to the different outcome in our population of ALS patients.

In conclusion, SNIP test could be a useful early indicator of tracheostomy in ALS patients.

Exploring reasons for the pattern of non-invasive ventilation (NIV) use among motor neurone disease (MND) patients: An interpretative phenomenological analysis

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Background: We have previously reported on psychological reasons for declining NIV. This study examines the psychological reasons for adherence to NIV among MND patients.

Methods: Six patients (male=5, mean age=59) who had used NIV for more than 6 months (mean 9.5, range 6-11 months) with ventilator interaction data were studied. Repeated interviews were transcribed and qualitatively analysed, using interpretative phenomenological analysis (IPA); IPA provides rich data to explore investigative phenomenon from a small sample.

Results: Out of the six patients, four patients used NIV consistently (mean±SD=22), while two patients used it less than 4 hours (mean±SD=31) per day. IPA suggests that good compliance (>4hrs) reflects the individuals’ attitude towards NIV use. Further analysis identified two influential factors: perceived essentiality and the perceived impact of NIV. The sense of need for NIV or knowledge of the benefits of NIV were not influential per se, but rather functioned as reinforcements to determine the pattern of compliance. Little change in the pattern of NIV use was observed over time, however this may be explained by other factors not evaluated in this study.

Conclusion: IPA suggests that the adherence to NIV is influenced by individuals’ attitude towards the use of NIV in terms of its essentiality and impact.

Grants from Motor Neurone Disease Association (UK).

NIV for MND in the West of Scotland assisted ventilation service (WoSAVS)

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Introduction: Motor neuron disease (MND) results in respiratory muscle weakness and respiratory failure (RF), with reduced quality of life (QOL) and survival. Non-invasive ventilation (NIV) effectively palliates symptoms related to RF, improving QOL, and survival (Boucke, Lancet Neurol 2006), and increasing use is reported. The SNIP test may predict need of tracheostomy, including age, sex, BMI, site of onset, time of diagnosis, co-morbidities, tobacco habit, traumas, sport activity, and sleep disorders breathing markers. Arterial Blood Gas analysis and respiratory functional test, including FVC, FEV1, as well as Sniff Nasal Inspiratory Pressure (SNIP) were also measured at first ambulatory control.

We found that SNIP test, at first control, positively correlated to the need of tracheostomy (p<0.001) in the entire population observed. The mean SNIP test value of the group who was admitted to tracheostomy was 25.12 ±25.25 compared to a mean SNIP value of 54 (25.46) in the group who did not undergo tracheostomy. Other anthropometric, clinical, functional, and nocturnal parameters evaluated did not correlate to the different outcome in our population of ALS patients.

In conclusion, SNIP test could be a useful early indicator of tracheostomy in ALS patients.
Chest wall volume changes during normocapnic hyperpnoea with constant tidal volume: A pilot study on laryngeal movements and inspiratory muscle coordination

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Introduction: Exercise induced vocalcord dysfunction (VCD) is a common condition, often confused with exercise induced asthma with unfortunate consequences.

Methods: Ten healthy subjects performed 1h of NH at 70% MVV (VT:2.6 ± 0.3 L; breathing frequency: 40 ± 1 breaths min−1) and cycled for 60 min at a fixed power output before and after 6 weeks of pressure-time integrals. The data suggest that aerobic exercise training in obese women improves chest wall volumes in CF and CG. All levels of PEEPs improve chest wall volumes in CF children’s.

Conclusion: Chest wall kinematics during different levels of positive end-expiratory pressure in cystic fibrosis children

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Objective: To study the effects of different levels of positive end expiratory pressure (PEEP) on compartmental chest volumes.

Methods: Twelve patients with CF (12±2.7 years, FEV1/FVC%: 81.3±6.6 and FEV1% (69±12) and ten age-matched healthy subjects (control group-CG; 11±1.8 years) with normal lung function. Both groups were evaluated by Optoelectronic Plethysmography in 3 minutes of quite breathing (QB), 3 minutes breathing against 3 levels of PEEP: 10 cmH2O, 15 cmH2O and 20 cmH2O.

Results: Both groups were similar during QB. Group intergroup analyses showed that the volume of chest wall was different between CF and CG at PEEP10 (Vcw=248.6±180.1 L vs 92.0±205.0 L, p=0.036; respectively) and at PEEP20 (Vcw=511.1±170.1 L vs 99.6±430.0 L, p=0.005; respectively). We found differences in respiratory rate between groups at PEEP20 (RR=22.6±7.4 vs.0.000, p=0.006), and PEEP20 (RR=37.2±19.3 vs 20.3±8.17, p=0.034). CF intragroup analyses showed that Vcw increased significantly in all levels of PEEP compared to QB (Vcw=286.0±0.79 L, VPEE=10= 0.487±0.181 L, VPEE1=0.515±0.21 L, and VPEE20=0.512±0.177 L, p<0.001), but no differences were found between PEEP levels. End expiratory lung volume increase in CF group during PEEP20 in comparison to QB (Vtocw=10.5±3.26 L vs 10.7±3.58 L, p<0.001), end inspiratory expiratory volume increase in all obese women pre- and post-aerobic exercise training programme performed at least 30 min per session; 3 sessions per week for 12 weeks. Results showed that aerobic exercise training significantly reduced body mass indices (BMI) (29.8±3.2 vs 23.9±2.8, p<0.001), e.g. absolute PImaxRV (126.1±22.1 vs 116.2±28.3 cmH2O), PImaFRC (119.8±6.2 vs 105.8±15.2 cmH2O), Pnsn (113.2±2.12 vs 98.1±21.2 cmH2O) and PImax (127.3±2.47 vs 119.8±6.26 cmH2O). The data suggest that aerobic exercise training in obese women studied appears to increase the RMS which may be, partly, a consequence of decreased fat mass and body fat.

Conclusion: Inspiratory rib cage muscles did not seem to take over work of the diaphragm. However, in- and expiratory rib cage muscles play an important role in preventing the development of rapid shallow breathing. Thus, RMT likely provides a training stimulus not only to the diaphragm but also to the rib cage muscles.

Support: SNF grant no. 32-116777.
The evidence base for conservative treatment is limited but two single-case reports suggest effects from inspiratory muscle strength training (IMST).

**Objectives:** To run a pilot study that objectively visualizes laryngeal response pattern(s) to controlled training with IMST.

**Methods:** To run a pilot study that objectively visualizes laryngeal response pattern(s) to controlled training with IMST.

**Conclusion:** The present work does not support the notion that the level of QF exists. However, individual DAF was found to be correlated with the workload of the finish (last 30 s) relative to the overall workload (R²=0.30; p=0.005).

**Results:** The average degree of ΔLDAf did not differ -21±2.12.8% (1STT) vs. -17.6±4.3% (2STT; p=0.22) while ΔLDAf of the shorter and more intensive test -34±0.5±5% (1STT) vs. -29.5±5.9% (2STT; p=0.04). Individual between-test differences of ΔLDAf did not correlate with those of ΔQF. However, individual ΔLDAf of both TT’s taken together significantly correlated with the workload of the finish (last 30 s) relative to the maximal workload (R²=0.30; p=0.005).

**Discussion:** On two different occasions on a long time period (6-7 months). TD was determined in one subject a paradoxical adduction was observed. Supraglottic adduction was seen in two patients at PLmax. In all subjects larynx moved downwards during inspiration, and nine of ten subjects seemed to engage all muscle groups in the hypo- and diaphragm during inspiration at PLmax.

**Conclusion:** The study suggests that IMST may be an efficient tool in the treatment of exercise induced VCD. Large interindividual differences suggest a need for further studies comparing groups, and underscores that objective methods must be used during instructions and training with IMST in these patients.
is in discrepancy with the relief of breathlessness after evacuation of effusions. We investigated changes in respiratory muscle strength before and after removal of several quantities of pleural fluid in patients with relatively large unilateral pleural effusions. We studied 49 patients (36 male & 13 female) aged 61±7.3 yrs. (mean±SD) with large unilateral pleural effusions of varying causes. Patients were selected on the basis of CT-scan not to have significant parenchymal lesions that would possibly interfere with lung physiological properties (e.g. tuberculosis effusions, neoplastic from extrathoracic primary site, hypoproteinemic effusions etc.). All patients were tested with an electronic mouth pressure meter, both before and 30 minutes after completion of thoracocentesis. The quantity of fluid removed was recorded for each patient and ranged from 0.38 to 1.4 L with a mean value of 0.82±0.25 L (mean±SD). Maximal Respiratory Pressures were recorded 3 times and highest values were selected for statistical comparison (paired t-test). Maximal Inspiratory Pressure before removal of fluid (MIPb) was 74±12 cmH2O while after (MIPa) was -88±13 cmH2O (p<0.01). Maximal Inspiratory Pressure before (MEPb) was 104±15 cmH2O while after removal of fluid (MEPa) was 121±17 cmH2O (p=0.01). We can conclude that removal of pleural fluid is accompanied by an improvement in respiratory muscle maximal pressures that may partly explain the relief of breathlessness after thoracocentesis.

P2114

Spinal behavior during tidal and deep breathing in healthy male subjects
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Spine has joint connections with all ribs and has muscle attachments with a part of diaphragm, suggesting a key role in respiratory mechanics. In this study, we aimed to investigate movement of the spine during tidal and deep breathing at a seated posture in which the spine was free from artificial restriction. Three-dimensional motion of the spine using an eight-camera system (60Hz) was performed in fifteen male healthy volunteers (mean age; 27±1.5 years). During tidal breathing, the spine moved very little (< 1 mm) while ventral parts of the ribs and the sternum well moved (1.5±0.2 mm) as “pump-handle”. Lumber spine moved toward ventral direction with deep inspiration to TLC while upper thoracic spine did with deep expiration to RV. These results suggested that spine was almost fixed during tidal breathing as the pivot of the ribcage. Breathing to RV or TLC recruited varieties of supplemental respiratory muscles, and transformed spine.

P2115

Positive effects of inspiratory muscle training (IMT) on ventilatory response to progressive hypercapnia in healthy subjects
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Inspiratory muscle training (IMT) is known to improve inspiratory muscle capacity, whole body exercise capacity and the sensation of dyspnea. Until now the effects of IMT on respiration during ventilatory stress, induced by hypercapnia, have not been examined. We speculate that IMT, by improving inspiratory pump capacity, may affect ventilatory response during CO2-rebreathing.

Aim of the study: The aim of our study was to analyze the effects of IMT on the ventilatory response during CO2-rebreathing tests in healthy subjects.

Methods: Eight healthy subjects (4 males, 4 females) performed specific IMT for 6 weeks. Maximal inspiratory pressure (Ps max) and endurance time during resistive breathing manoeuvres (lim) served as parameters for inspiratory muscle capacity. The ventilatory response to CO2, using the Read’s rebreathing technique, was analysed twice before commencement of IMT and once on the day after stopping IMT.

Breathing pattern during ventilatory stress changed in that the proportion of tidal volume on minute volume increased significantly. The peak histogram of the internal oblique abdominal muscle (BORG Scale) during CO2-rebreathing was analysed.

Results: After 6 weeks of IMT, inspiratory muscle capacity increased significantly. Maximal achieved VE (minute volume) as well as Vt (tidal volume) also increased significantly, while the level of dyspnea (Borg Scale) was lower. Breathing pattern during ventilatory stress changed in that the proportion of tidal volume on minute volume increased significantly.

Conclusions: IMT leads to more effective respiration under ventilatory stress, even in healthy subjects. This might be of clinical relevance for patients with lung diseases.

P2116

Maximum cough pressures are increased in patients with chronic cough
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Cough intensity can be defined with a variety of measures that include thoracic and abdominal pressure, airflow, electromyography and subjective scales. Little is known about cough intensity in patients with chronic cough. We investigated the physical characteristics of cough intensity in patients with chronic cough and normal subjects.

15 patients with chronic cough and 14 healthy subjects underwent measurements of esophageal pressure (Poes), gastric pressure (Pga), peak cough flow rate (PCFR), abdominal electromyographic activity and cough sound during voluntary coughs. The data from maximum cough efforts are presented. PCFR was normalised to predicted peak expiratory flow rate to account for gender and height differences. There was no significant difference in gender, age or lung function between patient and control groups. Maximum cough Poes was higher in patients with chronic cough than controls (188 vs 146cmH2O, p<0.02). This difference was limited to females only; the male group was underpowered to detect a difference. Cough Pga (p=0.01) and normalised cough flow (p=0.03) were also higher in female patients than in controls.

P2117

Obesity and respiratory muscle power
Randa Ibrahim1, Amit Bashir1, Aamir Magzoub1, Omer Musa2. 1Department of Physiology, Faculty of Medicine, El-Ismi El-Malhi University, Kosti, White Nile, Sudan; 2Department of Physiology, Faculty of Medicine, National Ribat University, Khartoum, Sudan

Introduction: In the past few decades obesity has become a global health problem. It could be a predisposing factor to a lot of cardiovascular, metabolic (such as diabetes mellitus) and respiratory problems that may result in pulmonary obstruction or restriction.

Objectives: The aim of this study was to investigate the effect of obesity on respiratory muscle power and so on lung functions.

Methods: This was a cross sectional study performed on 52 subjects (35 females and 17 males) in the age range 17-23 years in Khartoum state during the period February to May 2010. The body mass index (BMI) was computed following the standard equation (BMI kg/m^2) = (weight/height)^2. The percent of body fat was measured using Skinfold Caliber at the back of upper arm. Obesity was defined following the internationally accepted BMI cut-off points and ideal body fat percentages such as these from the American Council on Exercise. Pulmonary functions, respiratory pressure (Poes, Pga, PeFR, PEF) were measured using a micro-plus spirometer. Maximal inspiratory pressure (MEP) was measured using a pressure gauge. Statistical analyses were performed using the SPSS.

Results: The mean of MEP was significantly higher in obese subjects (p<0.00). The mean PEFR% was significantly higher in obese subjects (p<0.05). The mean FEV1/FVC% was significantly higher in obese subjects (p<0.01) but FEV1, FVC and PEFR values were not significantly different. A significant positive correlation was found between MEP and BMI and body fat% (obesity).

Conclusion: Maximal expiratory pressure was significantly higher in healthy obese subjects, compared to non obese control. possibly due to the increased work of breathing. Positive correlation between MEP and BMI and body fat% was observed.

P2118

Changes of active expiration respiratory muscle (RM) in men with chronic obstructive pulmonary disease (COPD)
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Background: For the present moment changes occurring in RM, during COPD, have been studied insufficiently.

Aim and objectives: to investigate the RM status and compare them with histological and subjective scales. Little is known about cough intensity in patients with chronic cough. We investigated the

All Patients Controls p-value

<table>
<thead>
<tr>
<th>All</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M-F</td>
<td>3.12</td>
<td>5.9</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>55 (17)</td>
<td>54 (23)</td>
</tr>
<tr>
<td>Poes (cmH2O)</td>
<td>188 (49)</td>
<td>146 (51)</td>
</tr>
<tr>
<td>Pga (cmH2O)</td>
<td>201 (38)</td>
<td>172 (60)</td>
</tr>
<tr>
<td>PCFR-predicted PEFR ratio</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poes (cmH2O)</td>
<td>181 (51)</td>
<td>132 (35)</td>
</tr>
<tr>
<td>Pga (cmH2O)</td>
<td>199 (40)</td>
<td>148 (44)</td>
</tr>
<tr>
<td>PCFR-predicted PEFR ratio</td>
<td>1.4 (0.4)</td>
<td>1.1 (0.5)</td>
</tr>
</tbody>
</table>

Presented as mean (SD).
Results: Contractions, small sites of a fragmentation, stratification of myofibrils and proliferation of fibroblasts were observed at the 1st and 2nd COPD stage. We revealed sclerotic of single muscular fiber and foci of sclerosis in intramuscular regions. The median H in the 1st and 2nd groups was 21 and 18 units respectively. Increasing severity of COPD was associated with enhancing of contractions and stratification of myofibrils. Thus, we detected the significant correlations between COPD severity and contractions (r=0.72) and with stratification of myofibrils (r=0.66). Indices H and SD were lower in pts with more severe manifestations (r = -0.42 and r = -0.59). Whereas index E was higher in these patients (r=0.59).

The paper significantly correlated with intensity of proliferation of fibroblasts (r=0.56).

Conclusions: Indices H, E, SD reflect the pathological processes occurring in RM in COPD patients.

P2119
Acute inspiratory load effects on chest wall volumes distribution and inspiratory muscles activation

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1Departamento de Fisioterapia, Universidade Federal de Pernambuco, Recife, Brazil; 2Department de Fisioterapia, Universidade Federal do Rio Grande do Norte, Natal, Brazil; 3Dipartimento di Biopiggeggers, Politecnico di Milano, Milano, Italy

Inspired loads can induce changes on the ventilatory pattern. In order to analyze the acute effect of the imposition of inspiratory load (IL) on the ventilatory pattern and inspiratory muscle activity, 39 healthy subjects (19M, 20F) were analyzed. Characteristics of male and female subjects respectively were: age, 25.50 ± 0.86 and 22.70 ± 1.53 years, FEV1/FVC, 95.05 ± 2.27 and 105.06 ± 1.97%pred; maxi-

mal inspiratory pressure, 123.6 ± 18% 50

Breathing Reserve 27

HRRU 44

HRrest 95

VCO2 Peak 0.97

P2120
Does lung transplantation improve chronotropic incompetence?

Matthew Bartels1, Hilary Armstrong1, Selim Arcasoy2. 1Rehabilitation & Regenerative Medicine, Columbia University Medical Center, New York, NY, United States; 2Pulmonary Medicine, Columbia University Medical Center, New York, NY, United States

Introduction: Chronotropic Incompetence (CI), or an attenuated heart rate (HR) response to exercise, has been widely established as a predictor of mortality but has not been studied in patients undergoing lung transplantation.

Objectives: We aimed to see whether CI in maximal exercise testing exists in patients with advanced lung disease before lung transplantation and improves after surgery.

Methods: A retrospective review of 153 patients who underwent lung transplantation at Columbia University Lung Transplant Program between 6/2002 and 6/2009. Patients had cardio-pulmonary exercise testing (CPET) within 30 months before or after transplant with concurrent with pulmonary function tests (PFT). Exclusion criteria included the use of beta-blockers. Comparisons were made with paired samples t-test.

Results: The mean PFT and CPET variables for the 71 patients (age 50±15 years) analyzed are shown in table 1.

Table 1. Select Pre/Post Transplant Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre Transplant</th>
<th>Post Transplant</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>24.1±4.29</td>
<td>25.9±4.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Watts Peak</td>
<td>46±29</td>
<td>84±34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VO2Peak</td>
<td>0.97±0.47</td>
<td>1.53±0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRrest</td>
<td>95±18</td>
<td>89±11</td>
<td>0.008</td>
</tr>
<tr>
<td>HRmax</td>
<td>175±21</td>
<td>135±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR85</td>
<td>442±23%</td>
<td>58±18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>272±18%</td>
<td>506±12%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Conclusions: Marked CI was observed before lung transplantation and improved afterwards but did not normalize. CI likely improved due to the normalization of pulmonary function post transplant. This was seen through a lower resting HR and a higher maximal HR. The implications of CI are not clear and warrant further investigation, including evaluation of the association of CI and mortality after transplant.

P2111
Does chronotropic incompetence occur in interstitial lung disease?

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Introduction: Chronotropic Incompetence (CI) is an attenuated heart rate (HR) response to exercise that has been widely established as a predictor of mortality in general populations and in patients with heart disease. CI has not been studied in patients with interstitial lung disease (ILD) despite abnormalities in pulmonary hemodynamics and cardiovascular parameters.

Objectives: Our primary aim was to see whether CI exists in patients with ILD during maximal exercise testing.

Methods: This is a retrospective review of 482 pts with ILD who underwent cardiopulmonary exercise testing (CPET) at Columbia University Human Performance Laboratory between 10/1999 and 2/2011. Patients had CPET with concurrent pulmonary function tests (PFT). Comparisons were made with paired samples t-test.

Results: The mean PFT and CPET variables for the 482 ILD patients (aged 56.6±11.0 years) analyzed are shown in table 1. Usual heart rate reserve used (HRUE) is 85% in normal subject populations. Mean PFT and CPET variables for the 482 ILD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>36.2±4.6</td>
</tr>
<tr>
<td>Watts Peak</td>
<td>42.2±22.5</td>
</tr>
<tr>
<td>VO2Peak</td>
<td>126±54</td>
</tr>
<tr>
<td>HRrest</td>
<td>89±16</td>
</tr>
<tr>
<td>HRmax</td>
<td>125±20</td>
</tr>
<tr>
<td>HR85</td>
<td>490±24</td>
</tr>
<tr>
<td>Breathing Reserve</td>
<td>42±17%</td>
</tr>
</tbody>
</table>

Conclusions: Marked CI was observed in patients with interstitial lung disease in a large cohort. This abnormality may have implications for long term survival as cardiac mortality and cardiac comorbidity are common as ILD progresses and possible development of pulmonary hypertension and right heart failure.

Further investigation with assessment of mortality risk and possible identification of interventions to improve CI may help to improve outcomes in this patient population.

P2122
Effect of posture on chest wall and diaphragm asynchronies in COPD

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In COPD hyperinflation alters the function of the inspiratory muscles. The zone of apposition of the diaphragm (ZOM) is reduced, thus COPD patients often show paradoxical movement of the lower rib cage. The aim of this study is to investigate if in COPD chest wall and diaphragm asynchronies are altered by posture.

Conclusions: Neither 0° RCP and RCA or 0° between RCP and AB was altered by posture in CT. Conversely, in COPD patients, 0° between RCP and RCA decreased when changing posture from ST to SP (θ=23.7°±19.5, 5.5±18.1 respectively, p<0.001).RCP and AB in COPD showed a behavior similar to CT while in ST (θ=0.3±13.3 in COPD, 0°±1°±4.5 in ST), but strongly differed in SP (θ=25.0°±18.2, p<0.001, COPD vs. CT). Moreover, in COPD AZOM was linearly correlated to RCP in ST (r=0.718±0.140), similarly to control subjects (r=0.729±0.150), while it was significantly less correlated to RCA (r=0.510±0.246, p<0.001). In COPD correlation between AZOM and both RCP and RCA decreased (r=0.530±0.244, r=0.511±0.230 p<0.05) in SP.

In COPD the diaphragm and RCA are uncorrelated in ST, but the synchronous action of the rib cage muscles and the diaphragm is similar to healthy. In SP the diaphragm is uncorrelated with both RCP and RCA, so the asynchrony with the rib cage muscles seems to be preserved.
Parasternal muscle contractility increases with aminophylline

**Introduction:** The traditional theophylline bronchodilator, Aminophylline, is still widely used, especially in the treatment of COPD. However, in COPD patients the effects of theophylline have been inconsistent. Recently, Aminophylline was shown to increase ventilation and costal diaphragm contractility in awake canines (Jagers et al. Respir. Physiol. 2009;167:273-280).

**Aim:** To investigate the effect of Aminophylline at therapeutic levels on the primary chest wall muscle, Parasternal Intercostal.

**Methods:** Sonomicrometry transducers and EMG electrodes were implanted in the left parasternal muscle. After recovery, the animals were studied awake, unaesthetized and breathing through a snout mask; air flow, ETCO2, heart rate, muscle length and shortening, and moving average EMG were recorded during room air, and CO2 stimulated breathing, before and after loading and continuous infusion of Aminophylline at therapeutic levels.

**Results:** For N=5 dogs (mean 31.1 kg) 24 days post implantation. Aminophylline serum levels were 66.4 μmol/L (therapeutic range 55-110). Minute ventilation increased significantly with Aminophylline: 6.7, 7.84, 11.8 and 16.6 L/min at room air, low (46), medium (52) and high (57 mmHg) CO2 stimulated breathing respectively. Parasternal contractility increased significantly.

**Conclusion:** Parasternal muscle contractility increases with greater muscle shortening per EMG, in awake, intact canines, at therapeutic levels of Aminophylline.

253. Lung and airway function

P2124

Relationships between bronchial obstruction and differential NO parameters after methacholine challenge testing

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The aim of the study was to investigate whether methacholine-induced changes of FEV1/FVC on the one hand, and of the alveolar NO concentration (Calv) and the NO flux from the bronchial wall (Jaw) on the other hand, are associated.

**Patients and methods:** 65 patients (all non-smokers) with work-related symptoms underwent a methacholine challenge test. Bronchial hyperresponsiveness (NSBHR) was defined as a decrease of FEV1 of 20% induced by methacholine. Measurements of FeNO were performed at five flow rates. Calv and Jaw were calculated.

**Results:** There was a positive association between lung function changes after methacholine challenge and Jaw decrease with a stronger Jaw decrease in the NSBHR group: ΔCalv: -0.73±0.27 vs. -0.25±0.07 mL, p=0.1. Contrary to this, Jaw increased in the NSBHR group (n=22) and decreased in the group without NSBHR (n=43) (ΔCalv: -0.34±0.1 vs. -0.2±0.07 ppb; p<0.001) with a significant negative correlation between the changes of FEV1/FVC and of Jaw in the NSBHR group (r=-0.65, p<0.005), but no correlation in the group without NSBHR.

**Conclusions:** The increase in Jaw in the NSBHR group is related to the degree of bronchial obstruction and evidently due to mixing alveolar and bronchial NO. The stronger airways obstruction (ΔFEV1/FVC), the more NO of bronchial source does not reach the alveoli and is exhaled deleter during the alveolar phase. Our results confirm the thesis of Högman et al. (2002), who interpreted elevated Calv of bronchial obstruction and evidently due to mixing alveolar and bronchial NO. The stronger airways obstruction (ΔFEV1/FVC), the more NO of bronchial source does not reach the alveoli and is exhaled deleter during the alveolar phase. Correspondently, elevated Jaw can be consided not only as a marker of alveolar inflammation but also as an indicator of peripheral airways obstruction.

P2125

Minor local alveolar edema in an in vivo human model can be detected by changes in respiratory mechanics by impulse oscillometry (IOS)

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**Aim:** We assessed the sensitivity of the impulse oscillometry methods (IOS) to detect residual alveolar edema in a lung segment after broncho-alveolar lavage (BAL).

**Methods:** 15 patients of both sexes undergoing BAL in different lobes for diagnosis of interstitial lung disease were studied: IOS was applied before and after withdrawal of BAL fluid, leaving in the alveoli a volume (V0) of 86.6±23.6 (mean ± DS), and continued up to 150 min. From IOS data we derived the corresponding values of respiratory resistance (Rrs) and reactance (Xrs) at frequencies from 5 to 35 Hz. We also estimated the “area of reactance” (Axx) as defined in Fig. 1A.

**Results:** After withdrawal of BAL fluid, the remaining V0 caused a 30% significant increase of Rrs at 5Hz: a significant increase in resonance frequency (fres) from 11.9 Hz ± 3.3 to 15.2 Hz ± 4.9; and minor changes in Xrs. The increase in fres led to a significant 90% increase in Axx. Rrs, fres and Axx returned towards baseline values through an exponential decay function within 150 min (data of Axx and regression equation are shown in Fig. 1B).

**Conclusion:** IOS technique is sensible enough to detect minor localized increase in extravascular lung water.

P2126

Acute changes in physiological parameters and pulmonary function during and after fiberoptic bronchoscopy

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**Background:** The short term effects of fiberoptic bronchoscopy (FOB) on physiological and pulmonary function parameters are not well known.

**Method:** Pulmonary function test was performed in patients before and within 30 minutes after bronchoscopy. Heart rate, blood pressure and oxygen saturation were recorded at the start of procedure and 5 and 10 minutes later.

**Results:** 55 patients were studied [39 males, mean (SD) age, 45.89 (13.77) years]. Mean (SD) BMI was 21.3 (3.82). 76.4% patients were non smokers and 16.4% were current smokers. Most patients were being evaluated for suspected carcinoma lung (27.3%), pneumonia (14.5%), interstitial lung disease (9.1%), Mediastinal lymphadenopathy (9.1%), carcinoma esophagus (7.3%) and fibrocavitary lesions (7.3%). The commonest complaints were cough (45.5%), shortness of breath (30.9), chest pain (12.7%), wheezing (7.3%), hoarseness of voice (7.3%), Hemoptysis (1.8%) and fever (1.8%). During the procedure there was significant increase in heart rate, systolic blood pressure and diastolic blood pressure while oxygen saturation declined. Post procedure there was a significant decline in FEV1, FVC, PEFR and FEF25-75 (Table).

**Table.** Changes in pulmonary function before and after bronchoscopy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre - FOB (mean ± SD)</th>
<th>Post – FOB (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>2.3±0.82</td>
<td>2.16±0.74</td>
<td>0.015</td>
</tr>
<tr>
<td>FEV (L)</td>
<td>1.73±0.70</td>
<td>1.52±0.66</td>
<td>0.004</td>
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<tr>
<td>PEFR (L/sec)</td>
<td>3±1.17</td>
<td>2.58±1.45</td>
<td>0.002</td>
</tr>
<tr>
<td>FEF25-75 (L/sec)</td>
<td>1.4±1.9</td>
<td>1.53±1.42</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Conclusion:** Bronchoscopy causes a significant acute decline in pulmonary functions. There may be thus, a justification for prophylactic use of inhaled bronchodilators prior to performing bronchoscopy.

P2127

Distribution and determinants of restrictive functional pattern

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A restrictive functional pattern is a common finding when performing spirometry; even in the absence of signs of pulmonary fibrosis or other disorders. This EPICS-SCAN sub-analysis (a population-based, cross-sectional study in eleven participating centres in Spain) aims to determine the frequency, geographic variation, individual consequences (respiratory symptoms, impact on activities of daily living) and “severity” of the restrictive functional pattern defined according to pre-BD spirometry as FEV1/FVC < 0.70 and a predicted FVC < 80% as per current ATS/ERS guidance. The prevalence of restrictive functional pattern was 12.7% (95% CI 9.7-15.7), with maximum in Seville (19.4%) and Madrid-La Princesa (15.7%), p < 0.05. Although the vast majority (97.1%) of participants with a restrictive functional pattern are objectively considered “mild” by spirometry (%predicted FVC 50-80%), they reported more plegmen, dyspnea, and wheezing than healthy, control participants, and in all SGRQ domains of quality of life and LCADL activities of daily living they scored worse (p < 0.05), actually, they scored similarly to participants with COPD in both (p > 0.05). In a multivariate analysis, only older age, male gender, lower education, and body mass index (BMI) ≥ 30.0 kg/m² were independently associated with having a restrictive functional pattern. We conclude that a restrictive functional pattern in spirometry is a common finding (12.7%), and with highly variable geographical distribution (range 3.7), whose population burden is important in terms of quality of life and activities of daily living and similar to that of an obstructive pattern compatible with COPD.

P2128
Effects of gastric bypass surgery compared to intensive lifestyle treatment on blood gases and lung function in morbidly obese subjects
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Objective: To aim for the effect of Roux-en-Y gastric bypass surgery (RYGBP) with intensive lifestyle intervention (ILI) on blood gases and lung function in morbidly obese subjects.

Design: One year non-randomized controlled clinical trial (ClinicalTrials.gov identifier NCT00273104).

Methods: 139 morbidly obese subjects, (103 women); mean (SD) age 44 (11) years. While body mass index 45.1 (5.6) kg/m², mean (SD) weight 131.8 (21.2) kg treated with either RYGBP (n=76) or ILI (n=63), were included. Blood gases and lung function tests were registered before and after treatment.

Results: Mean (SD) 1-year weight loss was 30 (8)% and 8 (20)%, and mean pO2 increased 1.4 (1.5) kPa and 0.8 (1.5) kPa in the RYGBP-and ILI-group, respectively (all P<0.001). Mean pCO2 decreased by 0.16 (0.4) kPa in the ILI-group (P=0.005), and 0.04 (0.5) kPa in the RYGBP-group (P=0.511). Mean ERV increased from 44 (32)% to 89 (39)% of predicted value (P<0.001) in the RYGBP-group, while there was no significant change in the ILI-group. We also found significantly improved mean values for FVC, FEV1, DLCO/VA, TLC, IC and RV in the RYGBP group (all P<0.001; data not shown). In the lifestyle group there were significant changes in mean TLC and RV (P<0.001), DLCO/VA (P=0.010) and FVC (P=0.049). There were no significant changes in mean DLCO in either group. There were significant between-group changes for mean FVC, FEV1, DLCO/VA, IC and RV in the RYGBP group, while there was no significant change in the ILI-group. We also found significantly improved mean values for FVC, FEV1, DLCO/VA, IC and RV (all P<0.001), TLC (P<0.007) and pO2 (P<0.032).

Conclusion: Blood gases and lung function improved in both treatment groups. However, the greatest effects were seen in the RYGBP group.

P2129
Reproducibility and repeatability of tidal breathing parameters derived from structured light plethysmography when compared to spirometry
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Background: Traditionally the “gold standard” for detecting abnormal vocal cord movement has been laryngoscopy. Novel dynamic 320-slice CT larynx has made it possible to quantify vocal cord movement non-invasively during inspiration and expiration. While spirometry has been useful in observing upper airway obstruction, little is known of its utility in identifying patients with abnormal vocal cord movement.

Aims: To identify changes in the flow volume curve in patients with abnormal vocal cord movement (AVCM).

Methods: Two groups comprising controls and asthmatics were recruited. Vocal cord abnormality was evaluated using 320-slice CT larynx. All patients had spirometry immediately prior to CT and relevant parameters were compared.

Results: AVCM was not found in healthy control subjects. However, it was present in 11/23 asthmatics (50%).

Discussion: While there was a significant difference in FEV1 between control and the two asthma groups, it identified obstruction alone. The only other discerning spirometric parameter was FIF50%/FEF50% which was significantly different between the control group and those with AVCM.

Conclusion: Spirometric parameters appear to be poor discriminators for detecting AVCM. It may be that more sensitive lung function measures, such a resistance measurement, may be required in order to further discriminate between obstruction of the upper and lower airways.

P2131
Compression artifact free flow-volume loops used to establish objective measurements in patient effort with spirometry
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Background: Flow-volume loops (FVL) measured by using pressure-compression volumetry plethysmography has been described in the literature and is commonly called compression artifact free flow-volume loops (FVLc). The utility of this technique has been to help demonstrate good patient effort and to help identify upper airway obstruction. There are no studies demonstrating measurable objective data to help confirm patient effort with FVLc.

Objective: Our study looks to identify the utility of FVLc by trying to establish a percentage cut off point for FVLc peak expiratory flow and what normal flow should be at 25, 50, and 75% intervals of the FVLc that can demonstrate good patient effort.

Methods: 76 patient’s charts that had FVLc in our lab were randomly reviewed. We looked to see if the peak flow on the FVLc was 25% higher than the traditional FVL. We recorded the flow percentages at the 25, 50, and 75% intervals of each patient’s FVLc. Patients were divided by having a peak flow greater than 25% (group A) or less than 25% (group B). We identified those patients with peak flows on the FVLc greater than 25% and 19 patients were less than 25%. Comparing groups, the flow at the 25% interval in group A were statistically higher (mean 0.58 vs 0.35, P<0.0001). All patients with peak flow greater than 25% had higher flow rates at the 25% and 50% flow intervals (P<0.0001).

Conclusion: Evaluating patient effort with FVLc may be helpful if the peak flow is 25% greater than seen on traditional FVL and if the 25% interval flow is greater. Further study is needed to establish the validity of this technique.

376s
P2132
Airway resistance during the methacholine challenge test: Comparison between plethysmographic and oscillometric technique
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3 Bioengineering, Politecnico di Milan, Milan, Italy

Background: Plethysmographic airway resistance (Raw) does not allow identification of bronchoconstriction site. Conversely, respiratory system resistance (Rs) measured by impulse oscillometry (IOS) can distinguish changes between peripheral and central airways mechanics (< 5 Hz for peripheral and 5-20 Hz for central airways). We wish to compare Raw to Rs in response to methacholine challenge (MCh).

Methods: 18 subjects underwent saline aerosol bolus (baseline) followed by increasing methacholine doses inhalation. At each dose, Raw and Rrs were measured respectively by body plethysmography and IOS. The measurements were repeated until reaching PD20 (estimated from FEV1) or the maximal dose (2400 g). We considered subjects with PD20 < 800.

Results: Rrs increased in all subjects during MCh. In 67% of subjects (group 1) Rs increased at 1Hz only, while in 33% (group 2) an increase in Rs was found at all frequencies. In group 1, unlike in group 2, the goodness of the regression between Rs and Raw (as from R²) was highest at 1Hz, waxing progressively with increasing impulse frequency.

Conclusions: Measurements of Rrs in the range 1-20 Hz allow to identify different sites for MCh response. The significant correlation between Rs at 1Hz and Raw in group 1 suggests that variation in Raw mostly reflects changes in small airways mechanics. In group 2 the significance of the regressions between Rs at all frequencies and Raw suggests that changes in airways mechanics of various calipers impact on plethysmographic measurements.

P2133
Impulse oscillometry (IOS) vs plethysmographic methods to detect PD20 in the methacholine challenge test
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Background: Methacholine challenge (MCh) test is the standard method used to unravel bronchial hyperresponsiveness. Airways resistance (Raw) is commonly measured with body plethysmography in addition to FEV1. The test is considered positive when a 20% decrease in FEV1 (provocative dose, PD20) is reached. We aimed to investigate whether respiratory impedance (Zrs) provides more sensible indexes, compared to Raw in detecting changes in bronchomotor tone.

Methods: 20 subjects underwent saline aerosol bolus (baseline) followed by MCh (50 to 2400 g). After each dose we measured 1) respiratory impedance (Zrs); at impulse frequency from 1 to 35 Hz) and corresponding values of respiratory resistance (Rrs) and reactance (Xrs); 2) Raw and FEV1.

Results: Fig. 1A shows that Xrs decreased at all frequencies at the methacholine dose preceding PD20 and even more at a dose higher than PD20. Due to the change in Xrs at low frequencies and to the increase in resonance frequency (fres), we considered the so called area of reactance (AXrs) as defined in Fig. 1B. We found that AXrs correlates significantly with Raw through an exponential function (Y = 0.1e4.55x), indicating that the growth in AXrs is larger than that of Raw, on increasing MCh.

Conclusion: Determination of AXrs through impulse oscillometry is more sensible than Raw and FEV1, to assess the increase in airway resistance during MCh.

P2134
Variability of respiratory rhythm and pattern of breathing changes in patients with bronchial asthma and cold airway hyperresponsiveness
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The role of control of breathing in modulation of bronchomotor tonus has been studied very little. It is unknown if there is a correlation between cold airway hyperresponsiveness (CAHR) and changes of respiratory regulation.

The aim of the study was to reveal the changes in respiratory rhythm and pattern of breathing and their correlation with bronchoconstrictor reaction to cold air hyper-ventilation in bronchial asthma (BA). 35 patients with BA and 6 healthy persons were examined. The group of BA patients was divided according to whether there was CAHR (14 patients) or there was not any (21 patients). CAHR was defined by 10% FEV1 fall after 3-minute isocapnic cold air (-20°C) hyperventilation.

Respiratory rhythm variability was evaluated by the value of mean-square deviation of respiration cycle duration during 15-minute interval. In result, a big variability of respiratory rhythm in BA patients with CAHR was revealed. Mean-square deviation was 0.86±0.13 vs. 0.56±0.06 in patients without CAHR (p<0.05). Significant changes in pattern of breathing in patients with CAHR were registered: inspiration shortening (0.37±0.01 vs. 0.41±0.01 s in healthy persons, p<0.01), expiration lengthening (0.63±0.01 vs. 0.59±0.01 s, p<0.01), respectively, at the absence of established differences in FEV1 between the groups. There was a direct correlation between FEV1 and tidal volume in healthy subjects and asthmatics without CAHR (r=0.89 and r=0.75, respectively, p<0.05). Patients with CAHR did not have such a correlation. The obtained data suggested a distinct interrelation-ship between the control of breathing and cold airway hyperresponsiveness in BA patients.

P2135
Improved survival with increased IC/TLC ratio, DLCO and FEV1 in an analysis of a COPD pulmonary function database
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Introduction: COPD is the fourth leading cause of death worldwide. FEV1 is predictive of COPD mortality. The IC/TLC is a measure of static lung hyperinflation. Aim: Analysis of a pulmonary function (PF) database evaluating the influence of FEV1, DLCO, IC/TLC and other variables on survival.

Design: Retrospective analysis of PF data base (31 year). 984 PF’s with a reduced FEV1/FVC, increased TLC and reduced DLCO were analyzed. The date of initial PF test was used as the initiation of the survival analysis. 596 patients had dates of death. Kaplan-Meier survival plots, in addition to Cox analysis, were performed to evaluate the relationship of age, FEV1 (GOLD stage), DLCO and IC/TLC ratio on survival, in addition multivariate analysis was performed assessing the effects of age, FEV1, gender, DLCO and BMI with the IC/TLC ratio.

Results: Cox analysis for the risk of death, revealed that a reduced IC/TLC ratio (< 25%) [HR 1.69, p<0.0001]; low DLCO (<22 predicted) [HR 1.28, p<0.043]; increased age [HR 1.035 for 5 year increase, p <0.0001] predicted death. Female gender [HR 0.692, p<0.692] and increased FEV1 (mild vs moderate) is predictive of survival [HR 0.69, p<0.0089]. Multivariate analysis revealed that age, gender, and IC/TLC (absolute ratio) remained the only statistically significant independent predictors of survival (HR=1.04, 95% CI: 1.03-1.04; HR 0.69, 95% CE: 0.60-0.83; HR 1.69, 95% CI: 1.34-2.13, respectively).

Conclusion: Analysis of a PF database reveals statistically significant associations of a number of measured and demographic variables with survival. IC/TLC ratio > 25, DLCO ≥ 22, Mild FEV1, Female gender, and BMI >25 is associated with survival.

P2136
Role of facemask spirometry in motor neurone disease (MND)
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In MND, NICE (UK) recommend considering non-invasive ventilation (NIV) when FVC values fall below 50% predicted. Patients with bulbar/facial weakness often fail to achieve a seal using a mouthpiece (tube). Thus tube spirometry may not fail to achieve a seal using a mouthpiece (tube). Thus tube spirometry may not reflect the patient’s true respiratory reserve. We have compared facemask (mask) to tube spirometry in 60 MND subjects recruited at a specialist clinic.

Methods: Spirometry was performed via mask and tube in random order. Since FVC is a maximal manoeuvre, a greater value was assumed to be more accurate. The Bland-Altman method of agreement between 2 measures was used. The bulbar component of ALSFRS r score was correlated to FVC values.

Results: The mean age was 64.6 (SD 10.45) years and M:F ratio was 1.5. Satisfactory FVC was obtained in all 60 subjects via mask, and 54 via tube. When bulbar ALSFRS r score <8, mask FVC was greater than tube. No difference in FVC seen when score >8. From the Bland-Altman plot, mask FVC was greater than tube in 86% subjects when FVC <2.5 L. Mask FVC was preferred by 73.9%. Of the 25 subjects with tube FVC >50% predicted, 32% had a mask FVC >50% predicted.

Conclusion: Mask spirometry provides a more accurate measure of respiratory
P2139
Pulmonary and liver injury after exposure to sublethal doses of microcystin-LR

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Rationale: Biological pollution caused by cyanotoxins leads to respiratory function impairment.

Aim: Study pulmonary mechanics, lung and liver histology in mice submitted to sublethal doses of microcystin-LR (MCLR) and evaluate whether the results depend on the doses.

Methods: Male Swiss mice were divided into 2 groups: CTRL (n=6) received distilled water intraperitoneally (ip, 100 mL) and TOX (n=30); injected with sublethal doses of MCLR (5, 10, 15, and 20 μg/kg ip in 100 mL of distilled water). 24 h later pulmonary mechanics [static elastance (Ea), viscoelastic component of elastance (ΔE), resistant (ΔP1), viscoelastic (ΔP2), and total (ΔPtot) pressures] were determined, and lungs and livers were prepared for histopathology. ANOVA was used to test differences among the groups.

Results: ΔP2, ΔE and ΔPtot were significantly higher than CTRL in all MCLR doses, but did not differ among them. Only TOX25 showed significantly higher ΔP2 than CTRL. Alveolar collapse was higher in TOX10 (18.95%), TOX15 (17.56%), TOX20 (19.11%) and TOX25 (21.63%) than in CTRL (11.57%). The lung inflammatory cell content (cells/mm3) gradually increased in TOX10 (12.90 ± 10^-3), TOX15 (14.90 ± 10^-3) and TOX20 (16.40 ± 10^-3) and TOX25 (5.30 ± 10^-3) in relation to CTRL (1.41 ± 10^-3). All TOX mice showed a complete loss of liver architecture by hyalinization, steatosis, dilated sinusoidal spaces and a high degree of binucleated hepatocytes. Necrosis began in TOX15, whereas only TOX 25 showed inflammation.

Conclusion: MCLR impaired pulmonary mechanics, lung and liver histology. These findings depended on the degree of exposure.

Supported by: FAPERJ, CNPq, MCT

P2140
Respiratory function in rats submitted to pharmacological hypothyroidism

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Hypothyroidism has been associated with hyperventilation, decreased respiratory muscle strength and fatigue. However, the impact of chronic hypothyroidism on respiratory mechanics has not been described so far. Male Wistar rats were divided in 3 groups: Control (C, n=3), hypothyroidism (H, n=5), and hypothyroidism + T4 replacement (HR, n=5). H and HR groups received 0.03% methimazole (MMI) in drinking water for 21 days, followed by saline or T4 (1 μg/100 g BW) injections daily during the last 10 experimental days, respectively. Then, respiratory mechanics was determined during spontaneous breathing [respiratory system (RS)] and under mechanical ventilation after muscle paralysis (RS, lung and chest wall). Total lipid content in bronchoalveolar lavage fluid (BALF) and lung histology were assessed. During spontaneous breathing, RS elastic recoil and inspiratory muscle pressure (Pmus,i) were lower in H group than in C (p=0.016 and p=0.011, respectively). The time required for Pmus,i to decay to zero was higher in H animals than in C or HR groups (p<0.001). Under mechanical ventilation, H group showed a smaller lung viscoelastic component of elastance (p=0.05) and viscoelastic pressure dissipation (p=0.042) than HR, and lower lung resistant pressure (p=0.015) than C rats. Chest wall and RS parameters did not differ among groups. H rats also showed a 3-fold increase in lipid content in BALF in comparison to C and HR rats. Alveolar collapse was less important in H group than in HR (p=0.026). Hence, in rats pharmacological hypothyroidism diminished RS impedance possibly because of an increased lipid content in BALF, and hormonal replacement could revert these findings. Supported by: PRONEX/FAPERJ, FAPERJ, CNPq, MCT

P2141
Exercise tolerance is related to lung density in patients with COPD

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In patients with COPD, the peak oxygen uptake (peakVo2) measured during cardiopulmonary exercise test (CPET) has been associated with lung hypoperfusion and survival. However, no study has compared exercise tolerance to quantitative CT measures of emphysema.

14 patients (10 females) with moderate to very severe COPD (FEV1 < 3.38 ± 8.5% pred; RV/TLC 53.6 ± 10.5%) underwent measuring of pulmonary function tests (F-V curve, static lung volumes, transferfactor of the lung for carbon monoxide) and breath-by-breath measurement of flow, volumes and O2 and CO2 concentrations during standard CPET. The extent of emphysema was assessed using the percentage of lung voxels with X-ray attenuation values less than -950 HU (%LAA).

Among pulmonary function tests the TLCO had the closest relationship to %LAA (p=0.0017), followed by the RV (p=0.0044) and the ratio of FEV1 to VC.
P2142

Exhaled nitric oxide and lung function in winter sports elite athletes

Samira Gasymova, Alexandr Ulianov, Lydia Nikitina, Fedor Petrovsky. Allergy and Clinical Immunology, Khanty-Mansiysk State Medical Academy, Khanty-Mansiysk, Russian Federation

Background: Little is known about the role of nitric oxide (NO) in pathogenesis of exercise-induced bronchocstriction and its association with lung function in athletes.

Aim: The aim of the study was to investigate whether airway NO is associated with lung function in elite athletes of winter sports.

Methods: A total of 86 elite athletes (biathlon, ski, ice hockey, snowboard) aged 14-35 were included in the study. FEV1, FVC, PEF (MasterScreen Pneumo, Viavys) were analyzed at the baseline and 1, 5, and 10 minutes after the exercise challenge test. NO was measured in the exhaled air (fractional exhaled NO (FeNO)) pre and between 1 and 5 min after the exercise using CLD 88 apparatus (EcoMedics). All tests were performed according to ATS/ERS recommendations before the competition phase.

Results: 21% of athletes had a post exercise decrease in FEV1 of ≥ 10%. Baseline and post exercise FeNO levels were 15.1 ± 1.6 ppb and 14.5 ± 1.5 ppb, respectively. Most athletes had a post exercise decrease in NOFeO (63.6% in males and 72.7% females). In athletes with the decreased post exercise NOFeO level, the mean change was 26.8% from the baseline, in contrast to 70% increase in those who had a post exercise NOFeO level unchanged or increased (p<0.01). We found the following correlations between (i) baseline FeNO and baseline absolute FEV1 (rs=0.41; p<0.01); (ii) post exercise FeNO and ΔFEV1 % in min post exercise (rs=0.38; p<0.04); (iii) post exercise FeNO and ΔFEV1 % 5 min post exercise (rs=0.58; p<0.01); (iv) post exercise FeNO and PEF% 5 min post exercise (rs=−0.56; p<0.01).

Conclusion: The present data suggest a role of airway NO in lung function and in exercise induced bronchoconstriction in elite athletes.

P2143

Exercise-related perceptions do not affect exercise response in subjects with OSA

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Lean and obese subjects have similar exercise capacity and intensity of dyspnea and leg effort. Obese individuals with OSA have a reduced exercise capacity [Vanbreke 2008], if this depends on exercise-related perceptions needs to be defined. Sixteen subjects with OSA, 8 lean (BMI<25.6±2.5) and 8 obese (BMI>30±4.1) and 14 subjects without OSA, 8 obese (BMI>44.9±7.5) and 6 lean subjects (25.6±1.6) underwent spirometry, polvomography, and incremental exercise test. FRC (9% pv) was similar in obese with and without OSA (84.4±9.8 vs 88.6±2.4 respectively; p<0.01) The volume of safety of OSA (AHE51±24 vs 30±10.5; p<0.05) was the same in obese and lean subjects. At VO2peak (6.26±0.6; 2.4±0.7; 2.51±0.6; 2.52±0.5 % in obese with and without OSA, and lean with and without OSA, respectively; ANOVA: p<0.05). VO2peak (ml/kg/min) was similar between obese subjects (OSA vs non OSA) and between lean subjects (OSA vs non OSA). End-expiratory-lung-volume (EELV) decreased in lean subjects with OSA (200±420ml), while increased in obese with (270±330ml) and without OSA subjects (304±330ml). Peak BORO was similar (ANOVA:p<0.05) in the four groups (7.5±1.6; 6.25±1.75; 5.9±2.4; 6.8±2.3 for obese OSA and non OSA, and lean OSA and non OSA subjects, respectively). Peak leg effort did not significantly differ in obese and lean subgroups: (8.63±1.69; 7±1; 4.21; 2; 8.5±0.8 for obese with and without OSA, and lean with and without OSA, respectively; ANOVA: p>0.05). The qualitative difference in EELV response indicates respiratory mechanical limitation during exercise in obese subjects with and without OSA. Exercise-related perceptions do not affect exercise response in obese with OSA.

P2145

Variability in walking patterns during the 6MWT in COPD patients and healthy controls

J. Annegarn1, M.A. Spruit1, H.H.C.M. Savelberg2, C. van de Boe3, A.M.W.J. Schols4, E.F.M. Wouters4, K. Meijer1. 1Program Development Centre, Ciro, a Centre of Expertise for Chronic Organ Failure, Horn, Netherlands; 2Human Movement Science, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands; 3Respiratory Medicine, NUTRIM School for Nutrition, Toxicology and Metabolism Maastricht University Medical Centre, Maastricht, Netherlands; 4Division of Exercise Science, University of Groningen, Groningen, Netherlands; 5Human Movement Sciences Department, University of Groningen, Groningen, Netherlands.

Aim: To assess if sputum inflammation and BHR contribute to functional exercise capacity (assessed by 6-Minute Walk Test (6MWT)) next to lung function, health related quality of life (HRQL) and health status in COPD.

Methods: 108 COPD patients (COLD stage II & III) participating in the GLUCOLD study [1] (81% male, median (range) FEV1%pred 64% (41-78), mean (sd) 6MWT-distance (6MWD) 551 meter (74)). Measurements at baseline: FEV1, methacholine, induced sputum, 6MWT, bodyplethysmography, RAND-36 and COPD COPD Questionnaire (CCQ). Variables tending to be associated with 6MWD univariately (p<0.020) were analysed using multivariate regression analysis with adjustment for age, height, gender, and FEV1.

Results: Higher RV%pred (b=−0.446, p=0.037), lower RAND-36 “Physical functioning” domainscore (b=0.888, p=0.043) and higher CCQ total score (b=−70.9, p=0.031) were independent contributors of lower 6MWD. Furthermore, higher age (b=−3.56, p=0.000) was associated with lower 6MWD. Induced sputum and PC20methacholine were not associated with 6MWD.

Conclusion: This study shows that increased sputum inflammation and BHR do not contribute to lower 6MWD in patients with moderate to severe COPD, yet markers of hyperinflation and health status are important determinants. A prospective analysis in this cohort will be performed to investigate if reduced inflammation causes less hyperinflation and improved exercise tolerance.


P2146

Variability in walking patterns during the 6MWT in COPD patients and healthy controls

J. Annegarn1, M.A. Spruit1, H.H.C.M. Savelberg2, C. van de Boe3, A.M.W.J. Schols4, E.F.M. Wouters4, K. Meijer1. 1Program Development Centre, Ciro, a Centre of Expertise for Chronic Organ Failure, Horn, Netherlands; 2Human Movement Science, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands; 3Respiratory Medicine, NUTRIM School for Nutrition, Toxicology and Metabolism Maastricht University Medical Centre, Maastricht, Netherlands; 4Division of Exercise Science, University of Groningen, Groningen, Netherlands.

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Conclusion: This study shows that increased sputum inflammation and BHR do not contribute to lower 6MWD in patients with moderate to severe COPD, yet markers of hyperinflation and health status are important determinants. A prospective analysis in this cohort will be performed to investigate if reduced inflammation causes less hyperinflation and improved exercise tolerance.


Table 1. Walking parameters

<table>
<thead>
<tr>
<th>6MWD (m)</th>
<th>SF (sec)</th>
<th>IMA (counts)</th>
<th>VC (%)</th>
<th>AC-ML</th>
<th>AC-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>672±85</td>
<td>1.10±0.07</td>
<td>813±68</td>
<td>615±18</td>
<td>0.67±0.12</td>
</tr>
<tr>
<td>COPD</td>
<td>494±78</td>
<td>0.96±0.09</td>
<td>5127±170</td>
<td>22.2±11.4</td>
<td>0.63±0.14</td>
</tr>
</tbody>
</table>

*: p<0.05

The model explained 84% (healthy) and 78% (COPD) of the variance in 6MWD. IMA and height were the only predictors of the 6MWD for healthy subjects but for COPD patients also age, SF, VC, AC-ML and AC-V contributed significantly (10%) to the variance in 6MWD

254. Clinical physiology for clinical problems
COPD patients use different walking strategies during the 6MWT than healthy control subjects which could be due to adaptations of both pulmonary and systemic impairments.

P2146
Exercise testing in the pre-flight evaluation of patients with cystic fibrosis
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Background: Due to hypoxic hypoxia, air travel may imply a health hazard for cystic fibrosis (CF) patients. Studies of other lung patients have suggested that exercise testing might help predicting in-flight hypoxemia. The aim of the present study was to identify pre-flight factors that might predict severe hypoxemia during air travel in adult CF-patients.

Methods: 30 CF-patients (20 patients, age 34±12 yrs, FEV1 59±25% pred (mean ± SD) participated in the study. Lung function tests, pulse oximetry (SpO2 level), arterial blood gas (PaO2 level), and a Hypoxia Altitude Simulation Test (HAST) breathing 15% oxygen were performed. In addition, 14 of the patients participated until exhaustion on a treadmill measuring PaO2, SpO2, maximal oxygen uptake (VO2max) and assessment of ventilation-perfusion mismatch defined as high V̇e/V̇CO2 at anerobic threshold.

Results: Five patient fulfilled criteria for supplemental oxygen during air travel based on BTS recommendations (PaO2 < 6.6 kPa or 50 mmHg). They all had FEV1 < 50% of predicted. Ten patients with a FEV1 < 50% of predicted had a negative HAST. The correlation between PaO2HAST and the following pre-flight variables were: SpO2max: r = 0.25 (p=0.23), SpO2rest: r = 0.515 (p=0.006), FEV1: r = 0.544 (p=0.002), PaO2HAST: r = 0.582 (p=0.001). The correlation between PaO2HAST and exercise variables was: VO2max: r = 0.638 (p=0.014), VE/VO2: r = 0.76 (p=0.001), PaCO2: r = 0.817 (p=0.001) and PaO2rest: r = 0.835 (p=0.001).

Conclusion: Exercise testing with measurement of oxygen desaturation and VE/VO2 may be useful tools in predicting the need for supplemental oxygen during air travel if HAST is not available.

P2147
Changes in operating lung volume and symptoms during daily activity in COPD
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Patients with COPD perform lower levels of daily physical activity and breathlessness and leg fatigue are symptoms limiting exercise. Less is known about symptoms and hyperventilation measured during laboratory exercise testing relate to daily activity.

We studied 20 stable COPD patients (15 male, mean (SD) age 67 (7) yrs, FEV1 0.96 (0.4) l, 36 (12)% predicted, IC 1.7 (0.4) l, 52 (16)% predicted during a time-limited endurance exercise test at 70% VO2 max. IC, dyspnoea and leg fatigue on a Borg scale were recorded every 2 minutes. We calculated the individual slope of the change in these variables expressed as IC absolute.

We assessed daily physical activity using both Actiwatch (AW) and SenseWear (SW).

There was a good relationship between AW mean activity score and AW mean activity moving (r²=0.7, p<0.01) and a close relationship between SW step count and AW mean activity score (r²=0.48, p<0.01). We found a good relationship between the AW mean activity score and the rate of increase of dyspnoea (r²=0.5, p<0.05) but no correlation between AW mean activity score and the rate of rise of leg discomfort (r²=0.2, p>0.05).

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Aktivity levels measured by these devices are similar and data registered with the same uniaxial leg accelerometer give similar level of daily activity. Baseline level of hyperventilation did not predict daily activity and the individual’s perception of breathlessness as lung volume rises is the important factor limiting daily activity. Changes in symptoms related to peripheral muscle dysfunction did not limit the daily activity in our COPD patients.

P2148
The transfer coefficient predicts the endurance increment when oxygen is given in COPD and lung fibrosis
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Background: Some but not all patients with COPD or interstitial lung disease (ILD) increase their endurance performance when supplemental oxygen is given.

Rationale: To find parameters that better predict oxygen response.

Method: We measured the effect of oxygen supplementation on the six-minute walking test performance (6MWD) in 59 COPD and 13 ILD patients. We compiled prediction models by means of multiple stepwise linear regression analysis.

Results: The percentage change in 6MWD was best predicted by the diffusion capacity, both in COPD (r = -0.43, p=0.0003) and ILD (r=0.75, p=0.001). The same applies for the absolute change in 6MWD in COPD (r = -0.44, p=0.0002) and ILD (r=0.71, p=0.002) patients.

Conclusion: The diffusion capacity appears to be the single best parameter to predict endurance response to oxygen in COPD and ILD and therefore might be used as a screening tool to select appropriate patients.

P2149
Impact of hemodialysis on dyspnoea in chronic renal failure patients
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Scarc reports exist on the symptom of dyspnoea in chronic renal failure patients. The aim of our study was to investigate the prevalence and severity of chronic dyspnoea in these patients and whether the severity of dyspnoea is different before and after hemodialysis. We recruited 25 patients with stage 5 (GFR<15ml/min) renal failure with (mean±SD age = 52±11 years, mean±SD duration of dialysis = 5±4 years, urea = 141±26 mg/dl, creatinine = 10±2 mg/dl. None of the patients suffered from any concomitant pulmonary disease. We used the modified (m) MRC scale to assess chronic dyspnoea. Routine lung function tests in seated and supine positions, closing volume (CV) with the single breath oxygen test, blood gases, Pimax, Pemax, P0.1, pattern of breathing were also measured. All of our patients (100%) complaint of some degree of dyspnoea before dialysis, which was significantly reduced after dialysis. The parameters that changed before and after dialysis were: Δ(mMRC) F= -0.5, (p<0.001), ΔWV6 pred, t= -3.1, (p<0.001), ΔHE (0.1±0.5, p<0.001), ΔTimaxpred (33.8, p<0.001), ΔCCC% predicted (0.2±4, p=0.032), and ΔPO1 (<240, p<0.001) cm H2O. Backwards regression analysis showed that the only single factor changed significantly after dialysis and correlates with Δ(mMRC) and ΔPO1 (r = 0.527, p<0.01). We conclude that hemodialysis improves dyspnoea by reducing central respiratory drive in patients with renal failure.

P2150
Effects of oxygen on exertional dyspnoea and exercise performance in patients with COPD
Kisuke Miki, Ryoji Maekura, Toru Hiraga, Hisako Hashimoto, Seigo Kitada, Mari Miki, Kenji Yoshimura, Yoshitaka Takeishi. Department of Internal Medicine, National Hospital Organization Toneyama National Hospital, Toyonaka, Osaka, Japan

Background: Accumulation of studying the oxygen (O2) response in chronic obstructive pulmonary disease (COPD) should provide important clues to the pathophysiology of exertional dyspnea. We investigated the exercise responses of hyperoxia on the dyspnea profile, as well as cardio-pulmonary, acidotic and sympathetic parameters in 35 patients with stable COPD.

Methods: The patients breathed 24% O2 or compressed air (CA) in random order during two incremental cycle exercise tests.

Results: The PaO2 and PaCO2 values were higher (P < 0.0001 and <0.05, respectively) at each exercise point while breathing 24% O2 compared with CA. At a standardized point in time near peak exercise, O2 reduced plasma lactate (P < 0.01). A similar peak minute ventilation/indirect maximum voluntary ventilation was observed between inhalations. At peak exercise, the dyspnea score, pH, and plasma norepinephrine were similar between inhalations. At each inhalation during exercise, the dyspnea - ratio (%) of the Δ oxygen uptake (peak minus resting oxygen uptake) curve reached a peak point that occurred at a similar exercise point between inhalations.

Conclusion: Breathing CA or hyperoxia, COPD patients did not develop ventilatory compensation for the exercise acidosis to stop exercise, re-

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The atmospheric pressure in cabin of the pressurized commercial aircraft is not equivalent to the pressure at sea level. If this hypobaric environment doesn’t trigger symptoms in most of people, the same is not true for patients with respiratory disease. Since the increase of air travel and the need to advise the patients to this particular setting, British Thoracic Society (BTS) has published recommendations to evaluate and prescribe supplemental oxygen in these conditions.

The present study describes 2 years’ experience in advice respiratory patients on flight fitness in Hospital Santa Maria.

During this period, 64 patients were evaluated (54% men, mean age 46±21 years) and underwent Hypoxia Challenge Test (HCT) with a protocol in agreement with BTS guidelines.

Physiological responses to the six-minute walk test in older adults

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Physiological responses to the six-minute walk test (6MWT) have been increasingly evaluated in patients with cardiopulmonary diseases. However, previous studies did not include healthy persons. The aim of this study was to evaluate age- and gender-related changes in physiological responses to the 6MWT and to establish a list of predictive equations for such variables. We evaluated 102 non-trained healthy older adults (48 men, aged 62±8) stratified in four age groups (40-49, 50-59, 60-69; ≥70). After familiarization, a third 6MWT was performed using a treadmill analyzer (k522) for assessing metabolic and cardiolpulmonary responses as well as oxygen uptake (VO2) time constant (tau) by an exponential fitting. Lean body mass (LBM) (impedance) and handgrip strength (HGS) were measured in 81 subjects. A set of linear equations was provided for prediction of the main physiological variables. The rate of gas exchange (Ri), VO2/heart rate (HR), deficit-VO2 and tau-VO2 were not affected by sex as well as total volume (VT); R and VO2/HR were not affected by age. Deficit-VO2 and tau-VO2 presented a tendency to age-related changes (p = 0.06). Several prediction equations adjusted by sex, age, height, weight, LBM, HGS, and 6MWT showed R2 values ranging 0.114 to 0.574 (e.g. deficit-VO2 and VT respectively). The best model for predicting VO2-peak was adjusted by LBM and age (R2=0.435). None of the variables studied was selected as predictive factors for tau-VO2. Therefore the prediction equations might provide a more appropriate frame of reference for normal physiological responses to the 6MWT in healthy older adults. Our results may be useful for better interpretation of walking performance in patients with cardiopulmonary disease.

Functional and neurophysiological aspects in patients with chronic obstructive pulmonary disease

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The neurophysiological alterations found in patients with chronic obstructive pulmonary disease (COPD) in combination with impairment of peripheral muscle, may further compromise functional activity of these patients. The purpose was to assess functional (balance and sit-to-stand test) and neurophysiological aspects (latency time the patellar and Achilles reflexes) relating these responses to the BODE Index. A cross-sectional study design was used to assess 22 patients with moderate to very severe COPD (>60 years) and 16 healthy volunteers as the control group (CG), performed measures of static and dynamic balance (pressure plate and Tinetti scale), monosynaptic reflexes (surface EMG), peripheral muscle strength (load cell) and SST. The inclusion criteria with COPD had a reduced reflex response to patellar 36.77±3.23 and Achilles reflex 43.54±6.60. Achieved a lower number repetitions on the SST 19.2±3.88, lesser peripheral muscle strength on the femoral quadriceps muscle, 24.98±6.88 and exhibit deficits in functional balance on the Tinetti scale 26.6±1.69, compared to the CG, all with p <0.05. The BODE Index demonstrated correlations with Tinetti scale, r = 0.59 (<0.05) and with the SST, r = 0.78 (p <0.05). The individuals with COPD had functional and neurophysiological alterations in comparison with control group. The BODE Index was correlated with the Tinetti scale and SST. Both are functional tests, easy to administer, low cost and feasible, especially the SST. The results suggest a worse prognosis; however, more studies are needed to identify the causes of these changes and the repercussions that could result in their activities of daily living.

Echocardiographic findings in severe chronic obstructive pulmonary disease

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1Department of Medicine, Hospital of Clinics – University of Buenos Aires; 2C.A. Buenos Aires, Argentina; 3Pulmonary Section, Instituto Argentino de Diagnóstico y Tratamiento, C.A.Buenos Aires, Argentina

Objective: To study the relationship between clinical, functional and echocardiographic findings in severe COPD patients who desaturate during 6MWT.

In normal subjects, ventilatory rate and oxygen ventilation (VO2) increases during exercise from a resting state until maximal levels are attained, whereas it seems that in asthmatic patients this increase is higher. The aim of the study was to evaluate the kinetics of VO2 during a constant-load exercise in a group of 11-16 y.o. asthmatic patients. 17 adolescents with mild stable asthma were studied. On the first day a progressive workload was applied to calculate the presumable aerobic threshold, which was assumed to be 90% of the maximum load tolerated. On the next day the subjects were asked to pedal at this constant load and the VO2 kinetics were studied using a k422 and a Cosmed® cyclogyrometer. In 9 patients (53%) there was an increasing trend of VO2 consumption, whereas in 5 (28%) this trend was not highlighted. In 3 patients (18%) data was unobtainable because of incompletion of test or non-cooperation. In conclusion, it was not possible to outline a common pattern of VO2 consumption, but in more than a half of our patients the behaviour of VO2 consumption during constant load was similar to that of the normal population.
Activity monitor outcomes in COPD – Assessment of variability of 6 monitors as part of the MJPI Reactive project

Zaferis Louvaris, Daniel Langer, Santiago Giavedoni, Yorgis Raste, Hans Van Remoortel, Eloisa Maria Gatti Regueiro, Frederick Wilson, Ioannis Vogiatzis, Nicholas Remoortel, Mario H. Rahnbohm, Barry Kiplinger, Thierry Troosters, Graeme MacIntyre, Daniel Langer, Richard Dekhuijzen

Department of Critical Care Medicine and Pulmonary Services, National and Kapodistrian University of Athens, Thora" son Foundation, Athens, Greece Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven, Belgium Physical Therapy Department, University of Federal de São Carlos (UFSCar), Sao Paulo, Brazil Respiratory Medicine, Laboratorio Broncopulmonar, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

Methods: We aimed to study the accuracy of 6 different activity monitors and their outcomes and their capability to detect less active days during Sundays, known to be less active days.

Results: We found a significant association between 6MW distance and 6MW SW (r=0.74; p<0.01), between 6MW and G2 saturation in the first minute walk (r=0.63; p=0.04). We also found a significant association between 6MW distance and COPD-SE (r=-0.39; p=0.08). No significant association between COPD-SE and GOLD and GOLD, FVC, MEP, MIP, DLCO, Tei Index, or basal SpO2 were observed.

Conclusion: We found a significant association between 6MW distance and COPD-SE. Additional studies are needed to confirm these results.

Results: Groups were similar in age, BMI, sex. Patients with severe SUBIMP had worse lung function, lower activity levels and more DH during ADL compared to patients with low SUBIMP (Table 1). Five of 15 patients with low SUBIMP showed DH during ADL, in contrast to 13 of 14 patients with severe SUBIMP (p=0.002). SUBIMP correlated with amount of DH during ADL (r=0.52, p=0.004) and physical activity level (r=-0.41, p=0.028).

Table 1. Patient characteristics and response to ADL

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low SUBIMP</th>
<th>Severe SUBIMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 % pred</td>
<td>67±10</td>
<td>50±20*</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>48±11</td>
<td>57±12*</td>
</tr>
<tr>
<td>activity level, YM1</td>
<td>94±15</td>
<td>85±12*</td>
</tr>
<tr>
<td>DH % decrease in IC</td>
<td>94±15</td>
<td>23±11*</td>
</tr>
</tbody>
</table>

Mean ± sd; *p<0.05 compared to Low SUBIMP ADL. Activity of daily life; DH: dynamic hyperinflation; FEV1: forced expiratory volume in 1sec; FVC: forced vital capacity; IC: inspiratory capacity; SUBIMP: subjective impairments; YM1: vector magnitude units.

Conclusion: Patients with severe SUBIMP show more DH during ADL. DH during ADL might increase breathing effort, which could play a role in the decrease in activity level observed in patients with COPD.

Methods: 18 GOLD 3-4 patients who desaturated during 6MW (SpO2<90%) were studied with pulmonary function tests and Doppler echocardiography, measuring tricuspid insufficiency peak speed and estimating systolic pulmonary arterial pressure (PAP) taking 35 mmHg as cut off to define pulmonary hypertension. Fisher’s exact test and t test of Mann-Whitney were used to compare numeric variables. Spearman correlation coefficients were calculated. p<0.05 was considered significant.

Results: Eight female and 10 male were studied, mean age 61.8±8 yrs, mean BMI was 24.75 (5) kg/m², mean FVC was 2.85±0.8, mean DLCO 45.5% (range=31-94), mean walked distance 315 m (range=120-480), the mean systolic PAP was 32.25±8.88 mmHg and 16/18 presented systolic PAP hypertension. Mean systolic PAP was 26.12 mmHg in 8 patients with BODE 2-4 and 37.37 mmHg in 10 patients with BODE 5 (p=0.0312).

No significant association between systolic PAP and GOLD, FVC, MEP, MIP, DLCO, Tei Index, or basal SpO2 were observed.

There was no significant association between 6MW distance and systolic PAP (r=0.41; p=0.048) or between DLCO and G2 saturation in the first minute walk (r=0.39; p=0.048).

Conclusions: We found a significant association between systolic PAP and BODE. Trends without significant association with systolic PAP and GOLD were observed. Further studies are needed to confirm these results.

P2157

Dynamic physical activity (DPA) level is an increasingly important clinical outcome in COPD research and management. In contrast to exercise capacity, the association of DPA with muscle function, health status and fatigue, has not been investigated extensively.

Aim: To investigate if DPA is associated with muscle function, health status and fatigue in severe COPD patients.

Methods: In a cross-sectional analysis we included 84 COPD patients (49 male, GOLD D1 (n=25), D2 (n=25), D3 (n=32), IV (n=22), mean age 59±11 years, FEV1 46±18% pred) who were entering a pulmonary rehabilitation program. DPA was measured with a pedometer (DigiWalker SW-200), muscle force with a handheld dynamometer and muscle endurance with the chair-stand test and the arm-curl test. Health status was assessed with the Groningen Activity Restriction Scale (GARS), Saint George Respiratory Questionnaire (SGRQ) and RAND-36, and fatigue with the Dutch Exertion and Fatigue Scale (DEFS).

Results: Mean DPA was 3302±2098 steps/day. Significant Spearman’s correlation (r=0.39) was demonstrated in Oxygen, Power and Cardiac variables at AT and ME.

Conclusion: Low DPA associates with lower muscle force and endurance, low physical functioning in mild to very severe COPD patients. Whether these variables contribute to the development of a low DPA level in COPD patients should be investigated in longitudinal studies.

P2160

Cardiopulmonary stress test: Determinations of oxygen consumption, power and cardiac variables at ventilatory threshold. Correlation with values at maximal exercise in COPD

Iván Caviedes, Rodrigo Soto, Paulina Gómez, Laboratorio Broncopulmonar, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

Background: In normal individuals a direct correlation exists between Oxygen consumption (VO2) and Power (W) measured at ventilatory threshold (AT) and maximal exercise (ME).

Purpose: To simplify cardiopulmonary stress test in COPD patients, demonstrating correlation of Oxygen, Power and Cardiac variables at AT and ME.

Methods: Prospective study of 44 COPD patients, mean age 63, mean FEV1 73.2%, mean FEV1/FVC 63.6% and mean DCO 56% of predicted. Cardiopulmonary stress test was performed calculating W, VO2, HR, VO2/HR, 3DVO2/W and reduction in Inspiratory Capacity (IC). Lineal regression was calculated between values at AT and ME.

Results: Patients ended the test due to dyspnea (Borg 5), reduction of Breathing reserve and IC (17%, -0.33L respectively). Mean Wmax, VO2max and AT of 74%, 85% and 50% of predicted respectively. Close correlation was demonstrated between VO2 and Power measured at AT and ME (r: 0.7 and 0.7 respectively), and between maximal HR and VO2/HR (r: 0.7 and 0.8 respectively).

Conclusions: A straight correlation was demonstrated in Oxygen, Power and Car-
P2161
Heterogeneous causes and degree of exercise limitation in COPD GOLD I and 2: Predictive value of CCQ and MRC
Frans Krouwels, Willemien Thijs. Pulmonology, Spaarne Hospital, Hoofddorp, Netherlands.

In COPD severity of disease is assessed with spirometry and dyspnea score such as CCQ (Clinical COPD Questionnaire) or MRC (Medical Research Council). Dyspnea scores and spirometry are poorly correlated, dyspnea may also be the result of other, not pulmonary, aspects, especially in COPD GOLD I and 2.

Questions: 1. What is the predictive value of CCQ and MRC with respect to the degree and cause of exercise limitation in patients with COPD 2. Which factors predict a pulmonary limitation?

Methods: 60 symptomatic COPD patients in a stable phase without relevant co-morbidity. At baseline they scored CCQ and MRC. A score of > 2 was considered abnormal dyspnea (D+), others were D-. Exercise limitation in a cardiopulmonary exercise test was labelled pulmonary (pulm), cardiac (card) or nonspecific (nonspec).

Results:

<table>
<thead>
<tr>
<th></th>
<th>D-</th>
<th>D+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCQ</td>
<td>0.25</td>
<td>0.15</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>MRC</td>
<td>0.40</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: In COPD patients GOLD I and 2 exercise limitation was not due to pulmonary factors in 86% and 43% of patients, respectively. Pulmonary or cardiac limitation can be expected at high CCQ or MRC score, and can not be excluded in patients with a low score.

P2162
The impact of anemia of chronic disease on exercise capacity among patients with chronic obstructive pulmonary disease
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Background: The presence of anemia has been associated with reduced performance in 6 minute walk test among patients with Chronic Obstructive Pulmonary Disease (COPD).

Aim: To investigate, for the first time, the impact of Anemia of Chronic Disease (ACD) on exercise capacity among COPD patients, utilizing cardiopulmonary exercise testing (CPET).

Methods: It is a case-control study. Cases (27 stable COPD outpatients who were identified to fulfill clinical and laboratory criteria of ACD) and 27 matched by age, height, sex, FEV1, and current smoking status non-anemic stable COPD patients underwent maximal CPET. Student’s T-test for independent samples was used for statistical comparisons between the groups; level of p<0.05 was considered significant.

Results: Cases (92.6% males; 64.8±7.8 years old, FEV1 % predicted=42.8±12.8) compared to controls (92.6% males; 65.3±7.2 years old, FEV1 %predicted=42.8±12.8) achieved lower: a) peak%predicted oxygen uptake (59.5±17.2 vs 71.3±11.9, p<0.01), b) peak work rate (67.5±24.9 vs 86.1±24.9 watts; p<0.05), c) peak%predicted work rate (54.9±21.6 vs 68.7±20.8; p<0.05), d) peak oxygen pulse (8.5±4.2 vs 10.4±2.9 ml/mins; p<0.05) and e) peak%predicted oxygen pulse (69.1±1.73 vs 82.4±18.2; p<0.01). There was also a trend for a lower%predicted aerobic threshold (>90±62%) in the group of cases. Rest gas exchange values and exercise parameters indicative of respiratory limitation (such as peak minute ventilation, peak respiratory rate and tidal volume to inspiratory capacity ratio) did not differ between the groups.

Conclusions: The presence of ACD significantly impairs the exercise capacity of COPD patients.

P2163
Tests of an intra-dialytic aerobic training program on oxygen uptake kinetics in patients with end-stage renal disease
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Background: End-stage renal disease (ESRD) is associated with several hemodynamic and peripheral muscle abnormalities that could slow the rate of change in oxygen uptake (VO2) at the onset and at the end of dynamic exercise. We therefore investigated the effects of supervised aerobic training during hemodialysis on the VO2 on- and off-kinetics in ESRD patients.

Methods: Twelve patients and 12 age- and gender-matched, non-trained patients underwent an incremental and constant load cardiopulmonary exercise tests by using a stationary cycle; three times a week.

Results: Training significantly accelerated VO2 kinetics (t decreased from 62.5±19.6 s to 45±12.6 s) and reduced O2 deficit at the onset of a sub-anerobic threshold (AT) exercise test (p<0.05). At a supra-AT test, t decreased from 52.9±17.4 s to 40±13.8 s (p<0.05) and time to exercise intolerance increased significantly (311±223.4 s vs. 589±235.8 s). Significant positive effects of training were observed at the off-exercise transient in both sub- and supra-AT tests (t=75±16.4 s vs. 66±20.8 s and t=73±20.4 s vs. 59±12.8 s, p<0.05, respectively). In contrast, VO2 on- and off-kinetics were significantly slower at the final evaluation in the non-trained patients (p<0.05).

Conclusions: A 12-week supervised aerobic training program was highly effective in accelerating on- and off-exercise VO2 kinetics at both moderate and severe exercise intensity domains in ESRD patients undergoing hemodialysis.

P2164
Influence of gas concentration and measurement interval on the reproducibility of non-invasive cardiac output determination by inert gas rebreathing in pulmonary healthy patients
Fredrik Tenkman, Matthias Sampaio, Ursula Hoffmann, Martin Borggreve, Jens J. Kaden, Joachim Saur. 1st Department of Medicine, Universitätmedizin Mannheim, Mannheim, Germany.

Background: Cardiac output (CO) is an important physiological parameter. In recent comparative studies non-invasive inert gas rebreathing (IGR) showed promising results. The aim of the prospective study was to evaluate the influence of gas concentration and measurement interval on the reproducibility.

Methods: We performed four series with two measurements for a gas bolus of 7.5%, 10%, 15% and 20% in supine position, respectively, and at intervals of 2 or 5 minutes. To rule out ventilation and diffusion disorders a bodyplethysmography was performed.

Results: A total of 384 measurements could be performed in 48 subjects, in 34 with an interprocedural interval of 5 minutes and in 14 of 2 minutes. For a fraction of 7.5% and an interval of 2 minutes we found a reproducibility of -0.8±1.1 l/min compared to 5 minutes with ±0.1±0.6 l/min (p<0.001). Rising gas concentration improved the reproducibility, for an interval of 5 minutes and a 20% gas bolus fraction no statistically significant clinical value was detected (p=0.88).

Conclusions: With an interval of 5 minutes a good reproducibility of the IGR measurements could be shown for all gas bolus fractions. For an interval of 2 minutes and low gas concentration we found a statistically significant reduced reproducibility. Using a 20% gas bolus the reproducibility reached the results of those of the 5 minute interval. This is particularly interesting for the determination of CO with a given small time frame, e.g. during spirometry. For the final assessment, however, additional studies with patients suffering from lung diseases are needed.
The hypotensive saline challenge (HSC) is a commonly used diagnostic tool to assess arterial baroreflex (AHR) and vocal cord dysfunction (VCD). Dyspnoea during testing is not uncommon and we postulated that oxygen desaturation may be a causative factor.

**AIM:** To document the degree of arterial desaturation during saline challenge and compare SpO2 changes in AHR, VCD and negative responses.

**METHODS:** SpO2 (Nellcor N595) was continuously recorded during 78 consecutive HSCs. SpO2 data was averaged over 32 seconds and minimum values used for analysis. Change in dyspnoea score (Borg) during the challenge was also recorded. Results were classified as AHR (change in FEV1 >15%), as VCD (change in MIF ≥20%) or negative otherwise.

**RESULTS:** Mean (SD) FEV1 was 86 (15%) predicted for AHR (n=20), 92 (18%) for VCD (n=18) and 94 (18%) for negative results (n=40). There was a consistent trend in SpO2 for all subject groups with significant desaturation during the final doses of saline and bronchodilatation (ANOVA p<0.001), and consistent resaturation during spirometric efforts. Mean (SD) maximum falls in SpO2 of 4.3% (2.7) were observed for AHR. 4.1% (2.0) for VCD and 4.4% (2.7) for negative results. There was no relationship between change in dyspnoea and degree of desaturation (p=0.43).

**CONCLUSION:** Hypotonic saline challenge causes a significant and reproducible pattern of arterial desaturation irrespective of the test response. These data would be consistent with progressive hyperventilation during HSC rather than indicating desaturation due to worsening ventilation-perfusion mismatching. Hypoxaemia does not appear to be the primary cause of dyspnoea during HSC.

**P2166**

A randomised cross-over clinical testing of portable oxygen concentrators in patients with COPD

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Portable oxygen concentrators (POC) deliver oxygen via intermittent demand valves (IDV). These merit comparison with standard continuous flow oxygen (CFO). We have performed a multicenter comparison of 4 POC in a cross over study in 74 patients with COPD (age 67±10, FEV1=41±20% predicted). Each patient tested one of 4 POC at rest and during a six minute walk test (6MW), with oxygen saturation recording (SpO2). Noise and discomfort were evaluated by visual analogue scales (VAS).

**RESULTS:** Mean 6MW distance was 388±114 with POC and 315 ±111±111 with CFO (p<0.06). However the distance walked with POC was clinically significantly less by (>10%) than CFO in 23% of patients and significantly better than CFO (by >10%) in 13.5% of patients. Dyspnoea during 6MW by VAS was identical for both types of device. 55.5% of patients had SpO2 fall with both devices and 27% no fall in SpO2. 33.5% had SpO2 fall with POC alone and 4% with CFO alone. Overall patients appreciated the POC because of security of oxygen supply. However, they judged POC oxygen delivery significantly less amenable and noisier than CFO.

**CONCLUSION:** 4 POC devices with demand valve oxygen delivery had similar efficacy to CFO devices but were noisier and less comfortable. Prescription of such devices needs to be individualized as regards settings for O2 delivery and patient comfort and lifestyle.

**P2167**

The compensatory mechanisms of loaded and unloaded breathing in exercising men

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To characterize the ventilatory responses to the resisting load or unloading, we studied the effect of breathing 79% helium – 21% oxygen (He-O2), 79% argon – 21% oxygen (Ar-O2) and 79% SF6 – 21% oxygen (SF6-O2) on the volume-time parameters, PETCO2, mouth pressure (Pml), work of breathing (Wb), central inspiratory activity (dP/dtI) and electromyographic activity of parasternal muscles in 10 normal subjects at rest and during 3 min steady-state exercise. There were no significant changes in tidal volume (VT), breathing frequency (f), inspiratory (TI) and expiratory (TE) durations, minute ventilation (VE) and PETCO2 when air was replaced by He-O2 or SF6-O2 at rest. VE and PETCO2 were not significantly different after replacement of air by He-O2 or SF6-O2 during exercise. However inhalation of He-O2 decreased in VT and increased in f, whereas inhalation of SF6-O2 led to opposite effects compared with air during exercise. Both at rest and during exercise, Pml, Wb, dP/dtI and EMGs were significantly less during He-O2 breathing and higher during SF6-O2 breathing from the first respiratory cycle after room air was replaced by He-O2 or SF6-O2. Ar-O2 breathing did not affect on time-volume parameters both at rest and during exercise compared with air. The increase in Pml, Wb, dP/dtI was observed at Ar-O2 inhalation during exercise relative to air. We conclude that internal resistive loading or unloading breathing changes the neuromuscular output required to maintain constant ventilation. The mechanisms of load or unloading compensation seem to be mediated by different im- plication in lung and respiratory muscle receptors as well as due to segmentary level reflexes and properties of the muscle fiber itself.
Results: Left ventricular end diastolic volume index in CBI correlated with echo-cardiography measurements in both M-Mode (r=0.6181; p<0.002) and B-Mode (Simpson, r=0.8431; p<0.001). Also the Stroke index in CBI correlated with the estimated stroke index in M-Mode (r=0.7077; p<0.001) and B-Mode (Simpson, r=0.7946; p<0.001).

Conclusions: In patients with IPAH or CTEPH, cardiac bioimpedance might be a useful tool to monitor left ventricular hemodynamics including left ventricular preload and cardiac output.

P2170

Relationship between pulse transit time and blood pressure during cardiopulmonary exercise tests

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Introduction: Pulse transit time (PTT), the interval between ventricular electrical activity and peripheral pulse wave, is generally assumed to be a surrogate marker for blood pressure changes. Although recent studies have affirmed the potential use of PTT in the diagnostic of sleep disorders and the monitoring of psychophysiological stress, little work has been published on the effect of physical exercise on PTT and results have been inconsistent.

Aims: To analyse PTT and its relation to blood pressure during cardiopulmonary exercise tests.

Methods: In 20 patients (mean age 51 ± 14 yrs, range 18-82) in a cardiopulmonary unit, ECG and finger-photoplethysmography were continuously recorded during routine cardiopulmonary cycle exercise tests. PTT was calculated for each R-wave in the ECG and the corresponding steepest upstroke in the photoplethysogram. For each subject the resulting PTT-curve was averaged in order to compensate sample rate and movement-associated variation, and values were compared to systolic (sBP) and diastolic blood pressure (dBP) in 9 predefined measuring points including measurements at rest, during increasing and maximum exercise as well as during the recovery period.

Results: Mean sBP and PTT at rest were 127 mmHg and 372 ms respectively, 197 mmHg and 287 ms under maximum exercise, and 132 mmHg and 365 ms during recovery. All subjects showed a significant, strong negative correlation between PTT and sBP (mean r = 0.97, range -0.99 to 0.93, p < 0.0001 to 0.015). The correlation between PTT and dBP with mean r = 0.41 (range 0.87 to 0.76, p=0.035 to 0.83) was rather weak.

Conclusions: These results indicate that PTT is a good potential surrogate measure for sBP during exercise.

P2171

Estimation of the ventilatory compensation point by the minute ventilation and heart rate relationship during exercise at high altitude

Gabriele Valli1, Paolo Onorati1, Dario Martolini 1, Alessandro Ferrazza 1, Gabriele Valli1, Paolo Onorati 1, Dario Martolini 1, Alessandro Ferrazza 1, Annalisa Cogo2, Paolo Palange1. 1Respiratory Pathophysiology, Department of Public Health and Infectious Diseases, University of Rome "La Sapienza"; Rome, Italy; 2Clinical and Experimental Medicine, Section of Respiratory Disease, University of Ferrara, Ferrara, Italy

We previously demonstrated that changes in the slope (∆) of increment in minute ventilation over heart rate (∆VE/∆HR) can be utilized for the detection of the ventilatory compensation point (VCOP) during incremental exercise at sea level (SL) (Onorati P, EustapioPhysiol, 2006). We hypothesized that the influence of hypoxic conditions, such as at high altitude (HA), on the VE and HR responses do not compromise VCOP detection using the ∆VE/∆HR ratio.

Methods: Six healthy subjects (42±14SD yrs) performed, on immediate ascent to M (Ex2), data of only 24 subjects are available, (5 AMS+; 19 AMS-) from Alagna (A), 1200m, to Capanna Regina Margherita (M), 4559m, with an overnight stay in Rifugio Gnifetti (G), 3647m.

To study the hypoxic profile and the AMS development during the ascent to M (Ex2) to reach G.

Introduction: Early desaturation during acute simulated HA exposure is significantly related to AMS+ group had a significantly lower SpO2 at rest and during HA exposure AMS+ group had a significantly lower SpO2 at rest and during HA exposure.

Conclusions: These results indicate that PTT is a good potential surrogate measure for sBP during exercise.

P2172

Lung diffusion at high altitude during exercise in high- and lowlanders

Maria Overbeck1, Jean-Benoit Marinot2, Claire De Bisschop3, Cristina Escotis4, Sofia Beloksa4, Herman Gropenhoff5, Mart Van der Plas5, Francisco Villafuerte6, Jose Luis Macarlupu5, Robert Narjie5, Herve Guenard8.

Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands; 2Department of Pneumology, OnzE Lieve Vrouwe Hospital, Amsterdam, Netherlands; 3Laboratory of Physiologic Adaptations to Physical Activities, Poitiers University, Poitiers, France; 4Reparto di Fisiopatologia Respiratoria, Università degli Studi, Bari, Italy; 5Department of Pathophysiology and Cardiology, Erasme University Hospital-Free University of Brussels, Brussels, Belgium; 6Pulmonary Diseases, OnzE Lieve Vrouwe Hospital, Amsterdam, Netherlands; 7Laboratoire de Physiologie Comparée, Faculté de Sciences et Philosophie, Universidad Peruana Cayetano Heredia, Lima, Peru; 8Laboratory of Physiologie, Medical Faculty, University of Bordeaux, Bordeaux, France

Introduction: Both the membrane (DM) and the capillary (VC) component of lung diffusing capacity (DL) have been shown to be increased in high altitude residents and to remain essentially unchanged in high altitude sojourners. Maximal exercise has been reported to decrease DM at sea level (Manier 1993). The effects of high altitude exercise on DM and VC as evaluated from the DL for carbon monoxide (DCO) and nitric oxide (DLNO) respectively, are incompletely understood.

Methods: Lowlanders (n=10) and highlanders (n=14) were tested at 3380m above sea level (Cerro de Pasco, Peru); lowlanders also underwent tests at sea level. Spirometry, alveolar volume (VA), DCO, DLNO. and VC were assessed (Hy-percaptop Medinof, Belgium) using the NOCO transfer technique. Values were corrected for PaCO2 and Hb and are presented as mean predicted value (Aguilaniu 2008) ±SEM. Measurements took place at rest and after an endurance test at 80% of VO2 max at heart rate returned to rest values.

Results: Spirometry was normal in all subjects. Hb nor SaO2 at rest were significantly different between the groups.

As regard the ascent to M (Ex2), data of only 24 subjects are available, (5 AMS+; 19 AMS-) from Alagna (A), 1200m, to Capanna Regina Margherita (M), 4559m, with an overnight stay in Rifugio Gnifetti (G), 3647m.

<table>
<thead>
<tr>
<th>H pre-E</th>
<th>H post-E</th>
<th>L pre-E</th>
<th>L post-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCO %</td>
<td>158±4*</td>
<td>151±4*</td>
<td>125±4</td>
</tr>
<tr>
<td>DLNO %</td>
<td>143±5*</td>
<td>154±7*</td>
<td>117±4</td>
</tr>
<tr>
<td>VmO %</td>
<td>143±5*</td>
<td>145±6*</td>
<td>120±6</td>
</tr>
<tr>
<td>VmL</td>
<td>133±5*</td>
<td>140±5*</td>
<td>110±2</td>
</tr>
</tbody>
</table>

H: highlanders, L: Lowlanders; E= endurance; *p<0.05 vs H; †p<0.05 vs. pre- vs. post-exercise.

At sea level, lowlanders did not demonstrate alterations in diffusion parameters pre- vs. post-endurance test.

Conclusions: Strenuous exercise in lowlanders resulted in a decrease of DCO which was probably caused by interstitial lung edema thickening the alveolocapillary membrane, whereas highlanders were capable of maintaining DICO-levels by an increase in DM.

P2173

Early oxygen desaturation is related to AMS development during acute exposure to high altitude (HA)

Luca Pomidori, Gaia Mandolesi, Giovanni Avracini, Eva Bernardi, Annalisa Cogo. Biomedical Sport Studies Center, University of Ferrara, Ferrara, FE, Italy

Early desaturation during acute simulated HA exposure is significantly related to AMS development.

Aim: To study the hypoxic profile and the AMS development during the ascent from Alagna (A), 1200m to Capanna Regina Margherita (M), 4559m, with an overnight stay in Rifugio Gnifetti (G), 3647m.

Methods: 44 (8F) subjects (age 18-67) were recruited in A, equipped with a 24-h data memory pulse oximeter (Pulsox-3Si, Minolta) and asked to fill the Lake Anima questionnaire (LL). Measurements took place at rest and after an endurance test at 80% of VO2 max at heart rate returned to rest values.

Results: Spirometry was normal in all subjects. HBO2 at rest were significantly different between the groups.

As regard the ascent to M (Ex2), data of only 24 subjects are available, (5 AMS+; 19 AMS-) from Alagna (A), 1200m, to Capanna Regina Margherita (M), 4559m, with an overnight stay in Rifugio Gnifetti (G), 3647m.

<table>
<thead>
<tr>
<th>A (rest)</th>
<th>I (rest)</th>
<th>Ex1</th>
<th>G (rest)</th>
<th>G (night)</th>
<th>Ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS+</td>
<td>94±1±6</td>
<td>84±4±5</td>
<td>81±3±9</td>
<td>84±2±1</td>
<td>76±7±3</td>
</tr>
<tr>
<td>AMS-</td>
<td>95±1±4</td>
<td>86±3±7*</td>
<td>82±1±5</td>
<td>86±1±9*</td>
<td>79±1±3*</td>
</tr>
</tbody>
</table>

In G, AMS+ always spent more time with a lower SpO2.

Table 2. % of total time

<table>
<thead>
<tr>
<th>At rest SpO2 ≤ 85%</th>
<th>Overnight SpO2 ≤ 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS+</td>
<td>56±2±1</td>
</tr>
<tr>
<td>AMS-</td>
<td>54±2±8*</td>
</tr>
</tbody>
</table>

As regard the ascent to M (Ex2), data of only 24 subjects are available, (5 AMS+;
The effects of pressure-threshold inspiratory load on lactate clearance after acceptable impedance signal can be obtained. Demonstrated that “qualitative” and “semi-quantitative” ICG might be useful to 0.05). This study and functional markers of disease severity and 1-year frequency of PAH-related deemed as “poor” in another 7 patients, i.e., technical problems were found in stroke volume (SV) and cardiac index (CI) were evaluated in 50 patients and 21 8) and 24% of the readings. Early decrease (N= 9) or a subsequent “plateau” in SV (N= 71/3 48 (± 22, 15 SV 1.5-fold were associated with other clinical and functional markers of disease severity and 1-year frequency of PAH-related adverse events (death and balloon atrial septostomy, 7; 0.05% but there were significant differences in mean minute ventilation per how athletes had a poor positive predictive value. RT and PE TBW were not determinants of EVH test result but a younger age and lower MVkg were related to a positive EVH test. Conclusions: 54% of elite athletes had a positive EVH test. AS athletes tended to have more positive tests. Symptoms perceived by athletes had a poor positive predictive value. RT and PE TBW were not determinants of EVH test result but a younger age and lower MVkg were related to a positive EVH test. Non-invasive estimation of cardiac output by impedance cardiography during incremental exercise in patients with pulmonary arterial hypertension Eloisa Ferreira, Roberta Palchini Ramos, Fernanda Nogueira, Jaqueline Sonese Ota Arakaki, L. Eduardo Nery, J. Alberto Neder. Medicine, Respiratory Division, Federal University of Sao Paulo, Sao Paulo, SP, Brazil Non-invasive monitoring of haemodynamic responses during incremental car-
diopulmonary exercise testing (CPET) could provide useful information on dis-
ease severity and prognosis in pulmonary arterial hypertension (PAH). Using an
impedance cardiography (ICG) device that does not require basal impedance or
blood resistivity estimations (PhysioFlow PF-03®, Manatec Biomedical, France), stroke volume (SV) and cardiac index (CI) were evaluated in 50 patients and 21 age-
and gender-matched controls during a ramp-cyclical exercise test on a cycle
exercise to 0 at minute 6 of the recovery period. At baseline, the slope of the HRRk was significantly higher in the control group (0.008) vs. 0.007 (p=0.001). The HRRk after a constant workload cycle ergometer exercise was recorded before and after 8 weeks of endurance training in 10 COPD patients (FEV1: 47±8%pred; 71±3 yrs) and 10 healthy controls (66±10 yrs). To calculate HRRk, the heart rate during the recovery period was normalized to range from 1 at the end of the activity to 0 at minute 6 of the recovery period. At baseline, the slope of the HRRk was significantly higher in the control group than in the COPD group (p<0.001). Thus, the HRRk at the first minute after exercise was lower in the COPD group (mean 1/3 beats) than in the control group (21 beats) (p<0.001). After training, the HRRk slope increased in the control group (from 0.009 to 0.012 (p<0.05) but no changes were seen in COPD patients (from 0.007 to 0.008)
We conclude that HRR kinetics after exercise enhances assessment of ANSd in
COPD supported. Supported by FIS PI061510; UE – FP7 (CIP-ICT) 225025.
Validation of a compact accelerometer for the measurement of physical activity in patients with COPD Yoshibi Minakata, Akiko Sugino, Manabu Nishigai, Masae Kanda, Kenichiro Akamatsu, Akiko Yamauchi, Kiyotaka Kita, Kazuto Matsunaga, Masakazu Ichinose. Third Department of Internal Medicine, Wakayama Medical University, Waka
yama, Japan
Background: The DynaPort Activity Monitor (DAM) has been reported to be useful to evaluate the activity in patients with COPD. However, its battery works for only several hours and it should be worn at two parts of body. A newly developed compact, single-position triaxial accelerometer (Actimarker) can measure the activity for more than 1 month, but has not been validated for patients with COPD.
Objectives: The validation of the Actimarker in patients with COPD was evaluated and the conditions of day for analysis were determined.
Methods: In study 1, the reproducibility of the Actimarker was evaluated for 14 stable COPD patients by comparing it with DAM. In study 2, the influence of holiday and the weather on the activity was examined. In study 3, the number of measurement days to ensure repeatability was determined.
Results: The differences in the activity by Actimarker and the locomotion by DAM were all within the limit of agreement at the intensity of ≥2.0 METs, ≥2.5 METs and ≥3.0 METs with Bland-Altman Plots. The durations of activity on holidays in patients with jobs and on rainy days were significantly shorter than those on weekends and on non-rainy days, respectively. The values of intra-class correlation coefficient were more than 0.8 in 3, 4 or 5 day-measurements, and the mean values of duration of activity from 3 or 4 days were all within the limit of agreement with Bland-Altman Plots.
Conclusions: The physical activity assessed by Actimarker was confirmed for its reproducibility and repeatability when the data from 3 non-rainy weekdays were analyzed. Actimarker seems to be useful as a simplified method to evaluate the physical activity in patients with COPD.

The effects of pressure-threshold inspiratory load on lactate clearance after maximal exercise Michael Johnson1, David Brown2, Katie Bayfield1, Javier Gonzalez4, Anael Barberan1, Alejandro Raimondi, Diego Agustin Rodriguez2, Gimeno Elena1, Arbilaga Anne1, VillarO Jordi1, Josea Josep1, Pulmonary Medicine - Pulmonary Function Laboratory, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain; 2Division of Nutritional Sciences, Federal University of Sao Paulo, Sao Paulo, SP, Brazil; 3Department of Cardiology, Hospital Universitari de Montreal, Montreal, Quebec, Canada; 4Department of Gene Therapy, Imperial College London, London, United Kingdom; 5School of Life Sciences, Northumbria University, Newcastle, United Kingdom; 6Department of Gene Therapy, Imperial College London, London, United Kingdom.

Chiappa, G.R. et al. (Med Sci Sports Exerc 2008; 40:111-116) showed that a 15 cmH2O pressure-threshold inspiratory load accelerated lactate clearance during recovery from intense exercise. However, we observed an effect only when the relative magnitude of the inspiratory load fell due to a training-induced decrease in maximum inspiratory pressure (Brown, P.L. et al. Med Sci Sports Exerc 2010; 42:1103-1112). This study thus tested the hypothesis that lactate clearance is influenced by the magnitude of inspiratory load applied in recovery from maximal exercise.

Eight male participants (VO2max 3.4±0.54 L/min) completed four maximal incremental cycling tests (20 W/min starting at 0W), of identical duration (16.2±0.2 min), followed by 20 min recovery comprising either passive recovery (PR) or breathing against an inspiratory pressure-threshold load of either 10 (IPTL10), 15 (IPTL15) or 20 (IPTL20) cmH2O. Arterialised venous blood samples were taken during recovery and analysed for lactate blood concentration ([La]B) every 2 min and blood pH every 4 min. During PR, IPTL10, IPTL15 and IPTL20 the [La]B after 2 min of recovery (11.2±1.9, 11.5±2.6, 11.2±2.0 and 11.2±1.8 mmol/L, respectively), the area under the [La]B curve during recovery (191±48, 192±55, 182±48 and 187±45 mmol, respectively), and mean blood pH (7.27±0.05, 7.28±0.05, 7.28±0.06 and 7.28±0.06, respectively) were not different between trials.

In conclusion, all inspiratory loads failed to influence lactate clearance after maximal exercise. Why inspiratory loading accelerates lactate clearance in some (Chiappa et al.), but not all (present study, Brown et al.), participants is thus unclear and warrants further exploration.
Physiological responses to the incremental shuttle walk test in healthy adults

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Physiological responses to the incremental shuttle walk test (ISWT) have been increasingly evaluated in patients with cardiopulmonary disease. However, previous studies did not include age- and gender-related factors in the prediction equations. The aim of this study was to evaluate age- and gender-related factors in the prediction equations for predicting physiological variables. The VO2 VT was used for measuring PA during a full week of daily living. Systematically varied bout lengths and interruptions are investigated to examine PA status.

Methods: Twenty COPD patients were selected from a larger dataset, based on a large range in PA level. The DynaPort accelerometer (100Hz, ±2g, McRoberts BV, The Hague, the Netherlands) was used for measuring PA during a full week of daily living. VO2 VT was determined using the ventilatory threshold (VT). VO2 VT was not affected by age as well as VO2/HR, RR, and VT were not influenced by age. There were no effect of age and gender in VO2 VT (% of peak VO2). Prediction equations adjusted by sex, age, height, weight, LBM, FM, HGS, and ISWT showed R2 values ranging from 0.352 to 0.661 (VO2 VT and VO2 max respectively). The best predictors of peak VO2 were HGS, weight, FM and age (R2=0.661). Age, weight, height and gender explained 59.7% of variance in physiological responses. The results therefore might provide a more appropriate frame of reference for normalcy of physiological responses to the ISWT in healthy older adults. Our results may be useful for better interpretation of walking performance in patients with cardiopulmonary disease.

Conclusion: This study shows that varying bout length and interruption duration has large impact on PA status. When applying PA recommendations this should be taken into account, particularly in subjects with a sedentary lifestyle.

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Physiological responses to the incremental shuttle walk test in healthy adults

Victor Dourado1, Ricardo Guerra1, Suzana Tanni2, Letícia Antunes3, Irma Godoy2.

1Department of Health Sciences, Federal University of São Paulo (UNIFESP), Santos, Brazil; 2Department of Internal Medicine, Botucatu Medical School (UNESP), Botucatu, Brazil; 3Rehabilitation Section, Botucatu Medical School (UNESP), Botucatu, Brazil.

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Conclusion: This study shows that varying bout length and interruption duration has large impact on PA status. When applying PA recommendations this should be taken into account, particularly in subjects with a sedentary lifestyle.
256. Epidemiology, diagnosis and treatment in obstructive sleep apnoea

P2184 The SHIP-Trend study – Epidemiology of sleep apnoea in Germany
Ingo Fietz1, Alexander Blau1, Isabella von Mengersen2, Sandra Zimmermann1, Beate Diecker1, Claudia Biro1, Iris Rieger1, Katharina Lau2, Anne Obst2, Henning Voelke3, Ralf Ewert3, Martin Glos1, Thomas Penzel3. Cardiology and Angiology, Center of Sleep Medicine, Charité, CCM, Berlin, Germany; 2Center of Internal Medicine, Cardiology and Pulmonology, Greifswald, Mecklenburg Vorpommern, Germany; 3Institute for Community Medicine, SHIP/Clinical Epidemiological Research, Greifswald, Mecklenburg Vorpommern, Germany

The SHIP-TREND study (Study of Health in Pomerania) is the first German population based study which implemented polysomnography (PSG) as one of the key investigations. 6000 inhabitants are drawn from the inhabitants registries. The main focus of SHIP-TREND is a full body MRI to evaluate the health status in northeast of Germany. An increased cardiovascular risk has been found in this region.

Cardiorespiratory PSG will be performed in all subjects between 20 and 79 years of age which agreed to participate. These subjects completed the Insomnia Severity Index (ISI scale), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and Restless Legs Syndrome Diagnostic Index (RLS-DI). Additionally all participants answered some specific questions about sleep duration and quality. Until December 2010 2769 volunteers entered the study and 966 of them underwent PSG. In a preliminary analysis 502 subjects were analyzed (225 female, 277 male). The mean age was 53.03 years. 117 of 502 subjects (23.3%) showed an apnoea-hypopnoea index (AHI) greater than 15 per hour sleep. There was a significant difference in gender when investigating the prevalence of obstructive and central apnoeas. Mean AHI in women was 7.2 per hour sleep and in men 13.4 per hour sleep. Independent of gender AHI increased with age.

There is a high prevalence of obstructive sleep apnoea in pommeranian population. Men showed more nocturnal breathing events than women. We detected in both groups a progression of breathing events with age. After completing all subjects the influence of BMI and comorbid conditions will be analysed.

P2185 Gender differences in sleep apnea severity are diminished during REM sleep
Maria Pallayova, Igor Peregrim, Zoltan Tomori, Viliam Donic.

Introduction: It has been shown previously that sleep apnea (SA) is substantially more common and more severe in men than women. Yet, the precise pathophysiological mechanisms accounting for gender differences in SA remain less well understood.

Method: A retrospective chart review was performed on patients who underwent in-lab polysomnography between January 2009 and December 2010 to examine the influence of gender on the polysomnographic features of SA. From 227 consecutive adults who met inclusion criteria, we identified 46 male-female pairs matched individually for age (mean±SD 52.4±9 years) and BMI (31.4±6 kg/m²).

Results: Despite similarities in age, BMI sleep efficiency, and Epworth Sleepiness Scale score, men had higher total apnoea-hypopnoea index (AHI) [median (interquartile range) 21.3 (8.6-43.4) vs. 8.8 (7.2-26) events/h; P<0.001] and the level of the AHI during NREM sleep [21.6 (8.5-43.7) vs. 7.4 (0.7-23.2) events/h; P<0.001] than did women. Men also had higher oxygen desaturation index [24 (10-53.1) vs. 14.8 (3.1-29.9) events/h; P<0.001] and lower mean nocturnal oxyhemoglobin saturation [93 (91-94) vs. 94 (92-95%); P=0.007]. Surprisingly, there was no statistical difference in AHI during REM sleep between men and women [21.3 (7-46.7) vs. 14.3 (2.1-45.8) events/h; P=0.662]. In addition, compared to men, women had a significantly higher difference between REM-AHI and NREM-AHI (P=0.023).

Conclusion: To conclude, SA is less severe in women than men because of milder SA during NREM sleep, which is independent of age and BMI. Our findings indicated that severity of SA is similar in men and women during REM sleep, suggesting differences between the sexes in upper airway function during sleep in adults with SA.

P2186 Gender differences in obstructive sleep apnea syndrome (OSAS): A clinical study (1308 patients)
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Background: Few studies focused on gender differences among patients with OSAS. The prevalence of hypertension was not elucidated after controlling for OSAS severity, age, and obesity grade in men and women, separately, and conflicting data were reported on the effect of gender on susceptibility to hypertension in OSAS.

Aim: To retrospectively assess gender-specific differences in patients with diagnosis of OSAS, with particular attention devoted to hypertension.

Methods: 1303 patients (20-90 years, 75% males) with symptoms suggestive of OSAS underwent overnight home polysomnography, and the apnea-hypopnea index ≥ 10 defined OSAS diagnosis.

Results: 73% of males and 56% of females had OSAS. Prevalences of obesity, metabolic disorders, and hypertension were significantly higher in females than males independent from OSAS. Females were significantly older than males only among the patients with the OSAS. The risk for OSAS was significantly higher in males than females only in middle ages (40-59 years). OSAS was associated with obesity in both males (Odds ratio, OR 3.01, 95% Confidence Interval 2.18-4.15) and females (2.70, 1.64-4.45). Severe OSAS was a risk factor for hypertension independent from obesity in males (1.67, 1.02-2.63, and 2.61, 1.50-4.54, for non obese and obese, respectively). OSAS, whatever it was its severity, was related to higher risk for hypertension neither in non-obese nor in obese females.

Conclusions: Although a clear male predominance, we found that with increasing age the prevalence of OSAS in women becomes comparable to that of males. Among OSAS patients, the male gender was related to higher susceptibility to hypertension.

P2187 Gender differences in sleep pattern in a cohort of patients with obstructive sleep apnea syndrome
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Introduction: Besides sleep related breathing disorders, other factors influence sleep pattern and polysomnographic parameters. Especially gender differences have been described that must be considered when making therapeutic decisions. Using data from a cohort of patients with OSAS, we will present gender related differences derived from a polysomnographic (PSG) examination prior to any therapeutic intervention.

Methods: Patients with OSAS who were referred to our sleep disorders centre with suspected sleep disordered breathing were monitored during the diagnostic visit and filled in the Epworth Sleepiness Scale. PSG recordings were visually analysed and parameters essential for sleep pattern rating were collected.

Results: Data from 938 patients were collected, consisting of 790 males (age 54.6±12.3 years) and 148 females (age 58.5±12.8 years) subjects. Sleepiness among genders was not different (males: 380 ESS<11, 410 ESS≥11; females 81 ESS<11, 67 ESS≥11; g=0.15). However, females had less breathing disorders (AHI 25±24.9/th per hour sleep; in males AHI 33±26.9/th; p<0.05). Percentage of N1 was lower in females than males (10.9±10.4 vs. 16±14.4%; p<0.01) while N3 was increased in females (19.9±10.7 vs. 16±10.4%; p<0.01). Corresponding to AHI values, arousal indices were lower in females than males (38±5.2 vs 21.2 and 44±4.5±3.1h; p<0.05).

Conclusion: We could show significant differences in light sleep and deep sleep proportions and arousal indices between male and female OSAS patients. In contrast, the proportion of sleepy patients was not significantly different. These results may help to understand gender related differences in reported daytime symptoms and facilitate therapeutic decisions.

P2188 Obstructive sleep apnoea/hypopnoea syndrome in middle-aged patients: Differences regarding the gender
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Introduction: It is well known that there are differences of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) regarding the gender in the elderly. The aim of this study was to evaluate the possible differences of OSAHS between middle-aged patients.

Methods: Three hundred and sixty five subjects, aged 45 until 65 years, suspected OSAHS were examined by full polysomnography, in our Sleep Laboratory the last years. Two hundred and ninety of them were suffered from OSAHS, 232 men, aged 53.75±5.72 and 58 women, aged 54.73±6.44 (±SD). The evaluated parameters were the daytime sleepiness (scoring by Epworth sleepiness scale), the apnoea/hypopnoea index (AHI) and the duration of nocturnal hypoxemia. The statistical analysis was done by “t-test” method.

Results: There were statistically significant differences between men and women regarding the body mass index (BMI) (34.08±6.74 vs 37.71±11.38 respectively.
Obesity Hypoventilation Syndrome (OHS) was defined as a BMI ≥30. 

Definitions: SAHS was considered when AHI ≥ 12/hour at breathing during sleep. 

Results: 82 out of 153 patients with DNV met the inclusion criteria. 53 (65%) women and 29 (35%) men. Values expressed by mean ± standard deviation were: Age at starting treatment: 72.4 ± 10.5 years, BMI: 37.5 ± 6.7; neck circumference: 41.9 ± 5.3 cm; ESS: 12.9 ± 4.1; AHI ≥ 12; BMI ≥ 30 and PaCO2 ≥ 35 mmHg at daytime; Excessive Daytime Somnolence (EDS) if Ewthop Somnolence Scale (ESS) score ≥ 12.

Conclusion: Half of the patients with DNV were ≥ 65 years old at the beginning of the treatment. All patients were obese and most of them, women. The most common cause of prescribing BIPAP was neuromuscular disease and the most common cause of change from CPAP to BIPAP was OHS.

Relation between obstructive sleep apnea syndrome severity and age

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Aim: To investigate the effect of age on severity of obstructive sleep apnea syndrome (OSAS) severity was the aim of this study.

Material and Method: The files of 874 OSAS patients diagnosed in our sleep laboratory between January 2005 – January 2010 were retrospectively analysed. Polysomnography was performed with Sleep Screen - Viasys device and scoring was done according to the criteria of Rech-Schaffen Kales. Chi-square and Pearson correlation coefficients were used to compare the groups. The significance level was set as p<0.05.

Results: There were 847 OSAS cases in the study. The mean age was 49.1±10.7 and of the cases, 602 (68.9%) were male, 272 (31.1%) were female. The prevalence of OSAS was mild in 235 (26.9%), moderate in 224 (25.6%) and severe in 415 (47.5%). A great majority of OSAS cases were belonging (65.2%) 40-59 years age group. Younger cases were 18.2% and older cases were ≥60.7% of OSAS patients. Mean AHI was 33.9 in younger (age<40), 36.8 in middle age (age40-59) and 42.4 in older (age≥60) group. Age >50 in 60.4% of mild OSAS cases whereas was the same in 50% of moderate OSAS and in 42.1% of severe OSAS cases. The severity of OSAS was statistically significantly increasing as age was advancing (p<0.05). As the cases were grouped as older and younger than 50 years of age, AHI, AI and ODI were statistically significantly higher and minimum saturation was significantly lower in older age group (p<0.05).

Conclusion: OSAS is getting worse as the age is getting advanced.

Treatment of sleep apnea over 21 months

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Objectives: 1) Analyse the evolution of the hours/day ratio of the use of CPAP in patients with sleep apnea hypopnea syndrome over a period of 21 months. 2) Study the factors related to poor treatment compliance (<3.5 hours/night).

Material and method: A total of 83 patients with sleep apnea hypopnea syndrome (AHI ≥22/h) treated with CPAP were included. The utilisation ratio of CPAP was recorded at 3, 6, 9, 12, 15, 18, and 21 months.

Anthropometric and socio-work variables were also recorded, as well as sleep and CPAP parameters, Epworth scale, morbidity and evolution.

Results: The ratio (hours/day) of real use of CPAP at 3, 6, 9, 12, 15, 18, and 21 months was: 4.9±2.3, 5.1±2.2, 5.3±2.5, 5.2±2.4, 5.3±2.5, 5.2±2.6, 5.2±2.5.

A univariate analysis and another adjusted by variables showed that the time of use did not significantly differ over the 21 months.

Conclusions: 1) The CPAP use pattern 3 months after starting treatment is stably maintained over a 21-month period. 2) Those who did not comply with treatment presented less serious sleep parameters, lower cervical perimeters, and lower prescribed CPAP pressure than those who complied.
Background: SDB has a high prevalence in the elderly population. OSA has been recognized in 7–18% of elderly people.

Aim: To evaluate the role of AT in the outcome of children with OSAS.

Methods: At the Department of Respiratory Medicine, Merlin Park University Hospital, Galway, Ireland.

Results: To date a total of 56 patients have complete data. Their mean BMI was 35.7 (±7.9), collar size 43.5 cm (±4.2) and 35 (63%) were male. Based on an AHI ≥ 15, 31 (55%) were diagnosed with significant OSAS. Those with OSAS had significantly higher BMI as well as collar size. The Epworth questionnaire (cut off 10) had a sensitivity of 77% and specificity of 52%, the Berlin 97% and 24%, respectively. STOP 100% and 28% and STOPBANG 100% and 12%.

Conclusions: If only patients with high risk scores were selected for subsequent PSG, 59% (Epworth), 13% (Berlin), 86% (STOP) and 93% (STOPBANG) of the patients would be tested. The STOP questionnaire resulted in the best sensitivity/specificity combination (if false negatives are unacceptable) but this would mean that 86% of the patients would have PSG but only 55% would have OSAS. No other combination of factors was found to improve specificity without a considerable decrease in sensitivity.

STOP is the simplest and most effective screening questionnaire to identify patients with OSAS and could reduce the need for PSG by 14%. A larger cohort is needed to confirm these findings and improve specificity of the questionnaires.

P2195 Follow-up of children with obstructive sleep apnea syndrome treated with adenotonsillectomy

Background: Hyperpertrophy of adenotonsilar tissue is an undisputed contributor to the development of OSAS in otherwise healthy children. A multicenter retrospective observational study shows the surgery approach has a resolution rate of about 27%. So it is important to identify children who will not resolve OSAS after adenotonsillectomy (AT) in order to plan an appropriate and integrated treatment for them.

Aim: To evaluate the role of AT in the outcome of children with OSAS.

Methods: Children affected by adenotonsillar hypertrophy, who underwent adenotonsillectomy for moderate-severe OSAS, were enrolled, from 2008 to 2009. All children underwent a complete clinical examination and overnight polysomnographic study before AT and after 12 months of follow-up.

Results: We included 21 children (mean age 4.09±1.76; M/F 17/4), with a mean body mass index –BMI– of 15.6±6.2 kg/m², with a mean apnea hypopnea index (AHI) of 5.9±8.8 ev/hr. Twelve children (57.1%) had malocclusions. After one year, 13 children showed a complete resolution of disease (61.9%) (AHI 0.3±0.3 ev/hr), while 8 children (38.5%) had a residual disease (AHI 2.6±1.1 ev/hr). Children with a residual disease had a higher BMI at baseline (16.5±3.7 kg/m² vs 15.4±1.1 kg/m², p<0.05) and a higher prevalence of malocclusions compared to those with a complete resolution (7/8 vs 5/13, X²=4.86, p<0.05). Stepwise multiple linear regression analysis identify malocclusions as the most important variable influencing the outcome (R²=0.24).

Conclusions: Although AT is the gold standard in children with OSAS and adenotonsillar hypertrophy, treatment of malocclusions need to be added to achieve a complete resolution of the disease.

P2196 Clinical reproducibility of the pediatric sleep questionnaire (PSQ)

Background: PSG is used for obstructive sleep apnea (OSA) diagnosis, due to its high cost is necessary to obtain clinical scores to evaluate the clinical reproducibility of OSA.

Aim: Evaluate the utility of the ACHaR as screening test for moderate/severe OSA in subjects recruited in an outpatient clinic.

Methods: Prospective study realized between January 2006 and December 2010. All patients enrolled were studied in a sleep center with PSG and also completed an easy to apply questionnaire (ACHaR). This test has 4 dichotomized variables: snoring, hypertension, neck circumference (cutoff = 40 cm), and reports of nocturnal gasping/choking; having a total score of 0-4 points. A score of 2 or more indicated high risk for moderate/severe OS (by PSG, apnea/hypopnea index ≥ 15).

Results: 753 adult patients (74.5% men) were studied (median age = 47.0 yrs). Using ACHaR, 646 patients (85.8%) were classified as high risk of moderate/severe OSA and 107 patients (14.2%) with low risk. The prevalence of moderate/severe OSA after PSG was different between these 2 groups: 72.4% (high risk) and 24.2% (low risk); p<0.001. The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and odds ratio (high risk vs. low risk) of the ACHaR score used as screening for moderate/severe OSA were, respectively: 94.7%, 31.2%, 72.4%, 75.7%, 72.9%, and 8.19 [95% CI = 5.09-13.16]. According to the receiver operating characteristic curve, the ACHaR score had area under the curve = 0.63 [95% CI = 0.58-0.67].

Conclusions: This study indicates that the ACHaR questionnaire was good sensitivity in detecting the patients with moderate/severe OSA.

P2197 The STOP questionnaire is the best screener for obstructive sleep apnea syndrome at the sleep clinic

Background: Polysomnography (PSG) is used for obstructive sleep apnea (OSA) diagnosis but is resource intensive and with restricted availability. Therefore we performed a pilot study to compare the Epworth, Berlin, STOP and STOPBANG questionnaires in their ability to identify OSAS confirmed by PSG among high risk patients. Additionally, cut off points to improve clinical detection of OSAS were explored.

Aim: To evaluate the utility of the ACHaR as screening test for moderate/severe OSA in subjects recruited in an outpatient clinic.

Methods: Prospective study realized between January 2006 and December 2010. All patients enrolled were studied in a sleep center with PSG and also completed an easy to apply questionnaire (ACHaR). This test has 4 dichotomized variables: snoring, hypertension, neck circumference (cutoff = 40 cm), and reports of nocturnal gasping/choking; having a total score of 0-4 points. A score of 2 or more indicated high risk for moderate/severe OS (by PSG, apnea/hypopnea index ≥ 15).

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Conclusions: This study indicates that the ACHaR questionnaire was good sensitivity in detecting the patients with moderate/severe OSA.

P2198 Questionnaire designed to identify patients with moderate/severe sleep apnoea and its correlation with polysomnography

Background: Sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) in the clinical pediatric population being evaluated for a potential sleep-related breathing disorder.

Aim: To evaluate the utility of the ACHaR as screening test for moderate/severe OSA in subjects recruited in an outpatient clinic.

Methods: Prospective study realized between January 2006 and December 2010. All patients enrolled were studied in a sleep center with PSG and also completed an easy to apply questionnaire (ACHaR). This test has 4 dichotomized variables: snoring, hypertension, neck circumference (cutoff = 40 cm), and reports of nocturnal gasping/choking; having a total score of 0-4 points. A score of 2 or more indicated high risk for moderate/severe OS (by PSG, apnea/hypopnea index ≥ 15).

Results: 753 adult patients (74.5% men) were studied (median age = 47.0 yrs). Using ACHaR, 646 patients (85.8%) were classified as high risk of moderate/severe OSA and 107 patients (14.2%) with low risk. The prevalence of moderate/severe OSA after PSG was different between these 2 groups: 72.4% (high risk) and 24.2% (low risk); p<0.001. The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and odds ratio (high risk vs. low risk) of the ACHaR score used as screening for moderate/severe OSA were, respectively: 94.7%, 31.2%, 72.4%, 75.7%, 72.9%, and 8.19 [95% CI = 5.09-13.16]. According to the receiver operating characteristic curve, the ACHaR score had area under the curve = 0.63 [95% CI = 0.58-0.67].

Conclusions: This study indicates that the ACHaR questionnaire was good sensitivity in detecting the patients with moderate/severe OSA.

P2199 Continuous positive airway pressure in patients with obstructive sleep apnea: A difference dependent on apnea/hypopnea index, leakage and mask pressure

Background: The Pediatric Sleep Questionnaire (PSQ) has 2 versions: a shorter one, which has been validated for sleep-related breathing disorders, and an extended version, which deals with wider range of disturbances. The Spanish version of the PSQ could be a suitable tool both for screening patients who require medical tests and for epidemiological research. Our objective was to evaluate its reproducibility in the clinical pediatric population.

Material and methods: 62 patients in pediatric age were gathered consecutively. 53% were male with a mean age of 5.15 years old (± 3.05) to whom a conventional polysomnography (PSG) was performed because of a probable diagnosis of SAAH. The 24 items of the PSQ (validated Spanish version for sleep-related breathing disorders) were completed at the Pediatric Outpatient Clinic and the night before the sleep study performed at the Respiratory Care Sleep Unit, both data were compared to let show discrepancies between PSG scores.

Results: The mean PSG score at the Pediatric Outpatients Clinic was 9.42 (± 4.77) and the previous score prior the PSG at the Sleep Unit was 8.7±4.59, with a correlation between both of 0.66 (p < 0.0001). The statistical concordance between the two determinations of PSG was moderate considering the cut line when 33% of the items were positive (kappa index 0.4, p = 0.003).

Conclusion: The PSQ score is highly variable when administered sequentially to a clinical pediatric population being evaluated for a potential sleep-related breathing disorder.
for obstructive sleep apnea (OSA). While a lot of studies analysed adherence of CPAP therapy in general, only little is known on adherence dependent on apnea-hypopnea index (AHI), leakage and mask pressure.

Methods: In a retrospective data analysis we determined age-dependent adherence of 4821 German patients (age = 58.4±11.2 years; 17.6% female, 82.4% male) treated with the CPAP device S8 (ResMed, Sydney, Australia). We studied AHI, mean mask pressure, mean leakage, hours of use per night and efficiency (days of use/total days).

Results: Mean therapy duration was 3.5±3.6 years. In the subgroups AHI<5, AHI=10–15 and AHI>15 patients used CPAP on average 36.8±37.8 min/day and days used/week (range 5.8 to 6.2) were similar. Furthermore, adherence was similar in the leakage subgroups <0.1 l/s, 0.1-0.2 l/s, >0.2-0.3 l/s, >0.3-0.4 l/s and >0.5 l/s in terms of hours used/night (range 361 to 380 min) and days used/week (range 6.0 to 6.2). Up to mask pressure of 14 cm H2O patients used the device on average 350 min, whereas patients with mask pressure >12-14 cm H2O used it more than an hour longer (415min). Moreover, there was a continuous increase between the lowest mask pressure subgroup (4-6 cm H2O) and the highest mask pressure (>14 cm H2O). Range was 5.7 to 6.5 days used/week.

Conclusions: Long-term therapy is high and long-term efficacy is excellent in long-term CPAP users. Adherence increases with mask pressure.

P2200

Importance of a questionnaire study on Latin American physicians about sleep apnea
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Introduction: We considered appropriate to investigate the knowledge and attitudes of obstructive sleep apnea among our physicians in the Latin American community.

Methods: Cross sectional survey study done in Ecuador. We previously translated the questionnaire obstructive sleep apnea knowledge and attitude (OSAKA) in English to Spanish.

Results: Out of the 284 questionnaires delivered just 193 (68%) questionnaires were returned. In a retrospective data analysis we determined age-dependent adherence of OSA. In the group 43-48 was 43, 2 if it is between 43 and 48, and 3 if it is >48 cm. We have considered 3 degrees of severity: 1 if the IAH is <5, moderate if it is between 15-30, and severe if IAH>30.

Results: The middle age of our patients was 50 (16-80); 78% males. The patient's percentage with different degrees of OSA's severity according to his CNP is expressed in the table.

<table>
<thead>
<tr>
<th>CPN</th>
<th>IAH &lt; 5</th>
<th>IAH 5–15</th>
<th>IAH 15–30</th>
<th>IAH &gt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;43 (n=61)</td>
<td>17 (28%)</td>
<td>22 (36%)</td>
<td>8 (13%)</td>
<td>14 (23%)</td>
</tr>
<tr>
<td>43–48 (n=112)</td>
<td>18 (16%)</td>
<td>24 (25%)</td>
<td>44 (39%)</td>
<td>37 (33%)</td>
</tr>
<tr>
<td>≥48 (n=164)</td>
<td>6 (4%)</td>
<td>30 (18%)</td>
<td>54 (32%)</td>
<td>94 (57%)</td>
</tr>
</tbody>
</table>

Conclusion: Physicians may have a lower accuracy due to high sympathetic activity in both states. Agreement was 0.91. For the second analysis agreement remained the same. Sleep stages, arousal and respiratory events were scored according to AASM criteria. ECG was analyzed by a special software (Hypnocore) which can provide a sleep evaluation and a respiratory event score by a new automated analysis. All patients were analyzed in two steps. The second analysis was performed on 54 patients after removing those with bad signal quality, arrhythmias and a total sleep time below 3 hours.

Conclusions: The results of this pilot study show the potential usefulness of the Internet as a tool for home monitoring of OSA patients and CPAP compliance improvement.

P2202

Web-based follow-up of CPAP compliance in obstructive sleep apnea syndrome: A pilot study
Valentina Isetta1, Carmen Leon2, Ramon Farn1,3,4, Josep Maria Montserrat1,4. 1 Unit of Biophysics and Bioengineering, Faculty of Medicine, University of Barcelona, Barcelona, Spain; 2Sleep Lab - Pneumology Department, Hospital Clinic, Barcelona, Spain; 3CIBER de Enfermedades Respiratorias, Ciberes, Barcelona, Spain; 4Institut d'Investigacions Biomèdiques August Pi i Sunyer, IDIBAPS, Barcelona, Spain

Introduction: Despite its fast penetration in many fields, the application of information and communication technologies in the clinical practice is still very limited, especially in respiratory medicine. The Obstructive Sleep Apnea Syndrome (OSAS) is a disease in which, because of its prevalence and chronic nature, telemedicine has a great potential.

Objective: To develop and to assess the feasibility of a web-based follow-up of continuous positive airway pressure (CPAP) therapy in OSAS patients.

Methods: An easy-structured web site was created for this study and each patient was given access to his/her own data exclusively. By visiting the web site, patients could answer to a weekly questionnaire about symptoms, sleep quality, potential CPAP side effects, physical activity and body weight, having the patient access to continuously updated temporal trends in graphical format. Moreover, informative documents about OSAS and CPAP therapy were available to free download.

Results: On a total of 163 consecutive patients of the Sleep Clinic, 66 reported minimum knowledge of the Internet and agreed to participate. After 12 weeks of monitoring, the participation rate was high (82%). In addition, patients responded to a satisfaction survey through the website, showing a level of agreement to the statement “Overall I am satisfied with the web service” of 4.2±0.58 points (1 = I strongly disagree, 5 = I strongly agree) and their potential interest in participating in a long-term web-based monitoring.

Conclusions: The results of this pilot study show the potential usefulness of the Internet as a tool for home monitoring of OSAS patients and CPAP compliance improvement.

P2203

Sleep disordered breathing detected by a new automated ECG analysis in subjects with insomnia
Thomas Penzel, Carmen Garcia, Martin Glos, Christoph Schoebel, Martina Sebert, Ingo Fietze. Interdisciplinary Sleep Medicine Center, Department for Cardiology, Charité Universitätsmedizin Berlin, Berlin, Germany

Patients with severe complaints of insomnia are sometimes investigated in a sleep laboratory in order to test for other causes of their complaints such as sleep disordered breathing or other sleep disorders. We investigated 64 patients with primary insomnia with cardiorespiratory polysomnography. Sleep stages, arousal and respiratory events were scored according to AASM criteria. ECG was analyzed by a special software (Hypnocore) which can provide a sleep evaluation and a respiratory event score by a new automated analysis. All patients were analyzed in two steps. The second analysis was performed on 54 patients after removing those with bad signal quality, arrhythmias and a total sleep time below 3 hours.

The analysis of respiratory events based on ECG in the group of 64 subjects resulted in 52 subjects (48 true negative, 4 false negative) with an RDI<5.12 subjects (10 true positive, 2 false positive) were scored with an RDI>5. The agreement was 0.91. For the second analysis agreement remained the same. Sleep stages in the second analysis were scored surprisingly good: 48.9% (ECG) vs. 48.7% (PSG) for light sleep, 15.7% (ECG) vs. 15.8% (PSG) for slow wave sleep, 14.9% (ECG) vs. 23.4% (PSG) for wake, and 19.9% (ECG) vs. 12.2% (PSG) for REM sleep.

Not many respiratory events occur in insomnia patients. These events are detected with a sufficient accuracy using the new ECG based algorithms. Sleep stage analysis based on ECG did show a good ability to distinguish light sleep, slow wave sleep, and wake/REM sleep. To distinguish wake and REM sleep by ECG alone has a lower accuracy due to sympathetic activity in both states.
P2204
Respiratory polygraphy versus polysomnography for the diagnosis of obstructive sleep apnoea in children
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Full attended polysomnography (PSG) is the gold standard for diagnosis of obstructive sleep apnoea (OSA). No consensus exists on the reliability of Respiratory Polygraphy (RP) for that purpose in children. This study aims to assess reliability between RP and PSG of determining sleep-related respiratory data in children. Twenty children with suspected OSA (10 yrs, 4-16) had full PSG performed in the Paediatric Sleep Centre, Robert Debre hospital, Paris, France. One investigator (IH) performed analysis using two modes in a random order: PSG mode (neurophysiologic and respiratory traces available) and RP mode (EEG, EOG, EMG not available on screen). Sleep was scored in PSG mode using Rechtschaffen-Kales criteria, and in RP mode using those of Moss et al (2005) which are mainly based upon variation of cardiac rhythm. Respiration was scored in the same manner for both modes using commonly accepted paediatric criteria. Intra-class correlation coefficients (ICC) were calculated.

When using PSG mode, total sleep time was 517 min (360-633), obstructive apnoea-hypopnoea (OAH) index was 6.3 (0.2-66) and minimal SaO2 was 86% (71-95). Low ICC was found for sleep data. There was some reliability between RP and PSG of measuring OAH index and minimal SaO2, but not of measuring mean duration of events and sleep time in OAH. These results prompt further studies to develop a higher number of children before determining recommendations of routine use of RP in children with suspected OSA.

P2205
Overnight oximetry as a screening tool for diagnosing obstructive sleep apnea in high altitude residents
B.N.B. Mahavera Prasad, C.A. Turkam, Medicine, Military Hospital Wellington, Wellington Barracks, The Nilgiris District, Tamilnadu, India

Aim: To determine the value of overnight nocturnal oximetry in strongly suspected cases of obstructive sleep apnea (OSA) among residents of high altitude.

Methods: This study is a retrospective analysis of prior overnight oximetry data of permanent residents staying at altitudes between 7000 to 8000 feet above the sea level who had a high pretest probability of OSA. The cases in this study were subsequently confirmed to have OSA by overnight sleep study (polysomnography). To determine the mean daytime and nocturnal oxygen saturation values for comparison with the study group, matched healthy non smokers residing in the area were studied by daytime and nocturnal oximetry.

Results: There were 12 males and 9 females in the study who had confirmed OSA. They were in the age group between 36 to 48 years. All had severe OSA. Nocturnal oximetry in these cases revealed more than 15 events of oxygen desaturation per hour of sleep with oxygen saturation falling more than 10 percent below pre-sleep awake baseline values. The awake oxygen saturation of all these cases were normal and were matching with mean value of 92 percent observed among 20 controls. The nocturnal oxygen desaturation among control group was less than 4 percent of awake values and events of desaturation were less than 5 times per hour of sleep.

Conclusion: Overnight oximetry is a useful screening tool in cases of OSA residing at high altitude areas. It can be used to confirm diagnosis of OSA in cases with a high pretest probability.

P2206
A new tool to help patients with obstructive sleep apnea syndrome (OSAS) make informed therapeutic choices
Nathalie Fleury1, Silvia Guiné2, Nicolas Kriczien1, Bernard Fleury1, 1CERMES, CNRS U8213 – INSERM U986 - EHESS - UPVD, Villejuif, France; 2Centre for Health Economics and Policy Analysis Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada; 3Sleep Unit, Hôpital Saint-Antoine, Paris, France

There remains concern that patients may not be fully informed regarding their mechanical treatment options for OSAS: continuous positive airway pressure (CPAP) or oral appliance (OA).

Objective: To develop a tool to help clinicians inform patients about treatment options, and to assess its validity, reliability and acceptability.

Methods: We developed a decision board (DB), to present information regarding the potential benefits and side effects of the 2 treatment options, using the best available evidence. To test validity, we evaluated in 34 healthy volunteers the extent to which the respondents’ preferences for a treatment changed predictably when the rate of effectiveness and side-effects were modified. Reliability was tested by re-administering the DB 2 weeks after (kappa test). The DB acceptability was evaluated in 68 consecutive patients newly diagnosed with OSAS, AHl=39 (22).

Results: In healthy volunteers, 58.8% chose OA, 41.2% chose CPAP. In the former group, 85% switched preference when the rate of effectiveness was reduced from 6/10 to 3/10, and 90% when the occurrence of occlusal contacts modification increased from 4/10 to 8/10. In the CPAP group, 57% switched when effectiveness was reduced from 10/10 to 5/10, and 42% when non compliance due to adverse effects increased from 3/10 to 6/10. Reliability was excellent (k=0.94). Concerning acceptability, 90% of the patients were satisfied with the information provided in the DB and 88% indicated that it helped them make a decision. The average score of true/false test of comprehension was 7/9 of 10 (range, 4 to 8).

Conclusion: The DB is a valid, reliable and acceptable tool to assess OSAS patients’ preferences.

P2207
Comparing different flow rates (20 and 35 l/min) under high-nasal flow therapy for the obstructive sleep apnoea syndrome (OSAS)
Georg Nilius1, Ulrike Domanskie1, Karl-Josef Franke1, Karl-Heinz Ruhle1, Hartmut Schneider2, 1Pneumology, HELIOS-Klinik Hugen-Ambrock, Hagen, Germany; 2Pneumology, John-Hopkins-University, Baltimore, United States

Introduction: We have demonstrated that 20 l/min nasal insufflation of airflow (HNF) can treat a subgroup of OSAS patients (Nilius G et al. Chest. 2010; 137:321-8). The aim of this study was to compare the effect of two flow rates (20 l/min (HNF20) and 35 l/min (HNF35)) on sleep disorders breathing. Methods: 18 CPAP naive patients (6 women, age 54±12 ±3.8 kg/m2, ESS 9.3±5.2) with more than 50% Hypopneas during a diagnostic night were recruited. During the treatment night both HNF20 and HNF35 were administered in a random order for a minimum of three hours each.

Results: The total event rate (AHI) in NREM/REM sleep was at baseline 5±37±3±2, at HF20 L/min 23±14±22±2 and at HNF35 L/min 19±13±15±6 (P<0.05 for REM). There were significant improvement HI but AI at 35 l/min versus 20 l/min in NREM and REM sleep. The lack of AI responses was associated with a significant increase in central AI (baseline vs HNF20 vs HNF35; 1 vs 8 events/hour). Nevertheless Oxygenation (T90) improved considerably with HNF35 compared to HNF20 and baseline in both sleep stages.

P2208
Variability in AHI and mean pressure over time in OSA patients treated with APAP
Siriram Chandramoulis, Dorothy Price, Jennifer Furlong, Syed Huq, Justine Hadercot, Dept of Respiratory & Sleep Medicine, Liverpool Heart & Chest Hospital, Liverpool, Merseyside, United Kingdom

Background: In patients with obstructive sleep apnoea (OSA), studies have shown that automatic positive airway pressure (APAP) treatment is comparable to continuous positive airway pressure (CPAP) in its cost effectiveness and efficacy. Patients with OSA are treated with APAP devices in our hospital.

Aims: Monitor changes in APAP and apnoea hypopnoea index (AHI) over a period of 3 months to identify factors which affect changes in mean AHI and APAP.

Methods: Symptomatic OSA patients [Epworth sleep score (ESS) > 10, AHI>10] were offered APAP therapy and monitored prospectively for 3 months. Data was downloaded at 2 weeks and 3 months and analyzed using paired t test and multiple regression.

Results: APAP therapy was initiated in 26 patients (22 men) with a mean (SD) age of 51 (11.7) years. Mean AHI was 44.5 (25.5) and mean Epworth score was 12 (4.7).

Changes in mean AHI and APAP are shown in the table.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>3 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI HI</td>
<td>9.2 (2.9)</td>
<td>14.2 (3.0)</td>
<td>14.2 (2.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Multiple regression identified baseline AHI as the only predictor of AHI change.
over 2 weeks and 3 months (p<0.0001) while a higher mean APAP at 3 months was also found to be significant (p<0.0003). Age, sex or body mass index did not affect changes in mean AHI or APAP.

Conclusions: In our study AHI was significantly reduced after 2 weeks’ treatment with APAP and continued to fall at 3 months even though mean pressure did not change noticeably. AHI change is greatest in patients with a higher baseline AHI and marked increase in pressure at 3 months. This could influence the onset of other factors such as change in upper airway muscle dynamics. Larger studies are needed to elucidate this complex relationship.

P2209

Manual vs. automated analysis of polysomnographic recordings in patients with COPD

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Background: Manual analysis of polysomnography (PSG) is time-consuming and computer systems have been developed to automatically analyse PSGs. Studies on the reliability of automated analyses in healthy subjects show varying results. In patients with Chronic Obstructive Pulmonary Disease (COPD) these studies have not been performed, while sleep quality can severely be disturbed in these patients. It is unknown whether automated analysis of PSG in patients with COPD provide accurate outcomes.

Methods: In a retrospective study the full-night polysomnographic recordings of patients with and without COPD were analysed manually and automatically. The outcomes of manual and automated analyses in both groups were compared using Bland-Altman plots, Students’ paired t-tests, and Pearson’s correlation coefficients.

Results: 50 PSGs from patients with COPD and 57 PSGs from patients with out COPD were included. In both study groups agreement between manual and automatic analyses was poor in nearly all sleep and respiratory parameters, like the total sleep time, sleep efficiency, sleep latency, amount of REM sleep, no. of arousals, and the apnoea-hypopnea-index.

Conclusion: Automatic analysis of PSGs in COPD patients have poor agreement with manual analysis when looking at sleep and respiratory parameters and should therefore not replace the manual analysis of PSG recordings in patients with COPD.

P2210

Heart rate analysis using multiscale entropy in OA patients under CPAP treatment – Pilot study

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One of the common effects of hypopnea/apnea events during sleep are arousals associated with heart rate change. Methods of nonlinear dynamics which analyze not only variability but also the complexity of the signal are the effective and reliable techniques used to analyze heart rate variability.

The aim of the study was to explore the possibility of detection of complexity changes of signal constructed from R-R intervals derived from ECG during full night PSG in OA patients (in whom apneahypopnea events were eliminated by CPAP therapy) using informative entropy.

21 patients undergoing routine diagnostic in sleep lab were recruited for the study (15 male, 6 female; age 52.4±9 years; BMI 35.8±3.0 kg/m²; Epsworth 13.4±5). The full night diagnostic PSG and the titration night using auto-CPAP under PSG supervisory (both according to AASM rules) were performed (diagnostic to titration time: 60±31 days). The CPAP therapy was well tolerated (the RDI change from 72±30 during diagnostic night to 5.9±6.9 during titration night. ODI from 61±31 to 3.8±4.1; AI from 50±26 to 6.5±4.3). The R-R intervals were detected in recorded ECG signal (250Hz), and the multiscale entropy (Goldberg’s MSE) was calculated for the scales 1-20.

In the low scales (up to 9) there were no significant difference between diagnostic and titration results. In the higher scales there were significant (p<0.05) differences.

The elimination of respiratory events has no significant effect on beat-to-beat heart rate complexity. However, using MSE analysis the results of eliminating heart rhythm changes associated with arousals are clearly visible.

P2211

Validation of a new polygraphy device for the diagnosis of obstructive sleep apnoea (OSA)

Ulrike Domanski1, K.H. Ruble1, Marguerit Laurent2, Maria Stoica2, A. Hosgeb1, M.P. D’Orthe1, Georg Nilus1, 1Klinik Ambrock, Universität Witten-Herdecke, Hagen, Germany; 2Groupe Hospitalier Bichat-Claude Bernard Assistance Publique, Hopitae de Paris, Universite Denis Diderot, Paris, France

Background: Snoring and OSA are such common problems that there is the potential to overwhelm the capacity of sleep laboratories. The goal of this study is to validate a new portable respiratory monitoring device (Alice PDX) against PSG during laboratory recordings, and to assess the devices ability to predict the presence of OSA in the home environment.

Methods: 45 suspected OSA patients (84.4% male, age 52.8±1.9 years, BMI 30.7±1.1 kg/m², neck circumference 43.3±0.8 cm and an ESS 9±±0.7) were randomized to receive the following diagnostic routines over 3 nights: 1 night with self applied Alice PDX, 1 night simultaneous in Lab Polysomnography (PSG) and Alice PDX recording, and 1 in Lab PSG. The data were anonymised and then manually scored according to AASM criteria.

Fifteen tests were used to compare each diagnostic modality to the reference in lab PSG, and correlation co-efficient calculated. Finally, the rate of diagnostic agreement was calculated.

Results: The Alice PDX was in diagnostic agreement with the simultaneously recorded reference PSG in 91.2% of studies. In 4.4% of studies the Alice PDX underestimated the AHI and on 4.4% of occasions the Alice PDX overestimated the AHI. Similar levels diagnostic agreement were observed when comparing PDx Home, and PSG Lab to the reference PSG recording.

Table 1

<table>
<thead>
<tr>
<th>AHI</th>
<th>P</th>
<th>c²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG Lam Sim* 17.6±3.2 15.9±2.6 0.2 0.85 &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDX Lab Sim 13.5±2.2 0.2 0.71 &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| PDX Lab 17.6±3.2 0.9 0.86 <0.0001 *

*Reference PSG.

Conclusions: The Alice PDX shows a high level of diagnostic agreement against PSG when used simultaneously and on a separate occasion at home. When used at home, the level of agreement is similar to a PSG performed on a separate occasion.

P2212

CPAP setting prediction in OSAS patients

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Aim: To determine how well anthropometric measures and data derived from a diagnostic polysomnography (PSG) study predict the CPAP setting required for therapy.

Methods: Data of 158 women and 592 men who had a diagnostic overnight PSG study, a diagnosis of OSAS (Apnea-Hypopnea Index (AHI) >5 and daytime somnolence) and a CPAP titration study were retrospectively analysed. Regression analysis was used to assess the predictive value of age, height, weight, neck, waist and hip circumferences, systolic and diastolic blood pressure at rest and diagnostic PSG data AHI, desaturation index, minimum (min) saturation, average saturation, average apnea-hypopnea duration for determining the required CPAP therapy pressure setting.

Results: Backward regression analysis identified AHI, neck circumference and min saturation as predictive parameters for the CPAP pressure. Age and BMI were entered at Step 1 hierarchical regression, explaining 6.1% of the variance in CPAP setting. After entry of AHI, neck circumference and min saturation in Step 2 the total variance explained by the model as a whole was 19.5%, F(5,697) = 35.08, p<0.0005. The three control variables explained an additional 13.8% of the variance in CPAP therapy pressure, after controlling for age and BMI.

Conclusions: OSAS severity, neck circumference and overnight minimum saturation have a statistically significant contribution of 19.5% on the variance of the CPAP therapy pressure, independently of the age and the obesity of the subject.

P2213

Capsaicin-induced cough reflex is inhibited by deep inspiration in children with mild asthma

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Background: Asthma is characterized by bronchospasm accompanied with frequent coughing, the pathogenesis of which is not clear. In healthy adults deep inspirations (DI) provide a protective effect against bronchoconstriction triggered by methacholin, which correlates with the number of accompanying cough efforts. In adult asthmatics DI have some spasmolytic effect, which decreases with age and severity of the disease. Our aim was to test the elicibility of cough reflex by capsaicin in children with mild asthma and their presupposed inhibition by DI.

Methods: In 21 children (8 girls and 13 boys of mean age 13.3 y) with mild asthma (FEV1 >80%) the cough reaction to inhalation of increasing concentrations
of capsaicin from a compressed air-driven nebulizer manifesting with 2 and 5 or more cough efforts (C2 and C5) was tested. The effect of previous DIs was also examined. Results: In control conditions 20.86 (14.58-29.8) umol/l of capsaicin provoked no detectable respiratory events. In-laboratory polysomnography (PSG) according to the recommendations of AASM. RERAs were identified by a flattening of the airflow registered by nasal cannula and/or a visible increase in thoraco-abdominal effort leading to an arousal. All PSGs performed during a period of 6 month with an apnea/hypopnea index of less than 15/h were reanalyzed by a single sleep specialist. Patients (pts) demonstrating RERAs in more than 50% of all breathing events were included for further study. Within 303 sleep studies a total of 45 pts were included (14,8%), mean respiratory disturbance index 17.4±10.4/h. 71% were male, with a mean age of 54,6±14.8 years. In 42% of the pts sleep latency and in 63,8% sleep efficiency (mean 78.5±12.6%) were reduced. Decreased slow wave sleep was found in 55%. In 61% a reduced REM sleep was found and all pts had a high arousal index (41±18/3hr).

The pts included in our sleep clinic 50% showed an increased epworth scale (12±6.5), 36% were hypersomnolent and in 75% (BMI=30±6.9) pts the results of a positive therapy questioner (ptt) with improvements of symptoms (ESE=<8) and good adherence. Contrary to other data we found a high% of males within the pts with mainly RERAs in PSGs. As a conclusion, pts with RERAs should be evaluated for EDS for therapy with ptt improves daytime symptoms and is reasonably well tolerated.

P2217

Efficacy of the “tennis ball technique” in patients with positional obstructive sleep apnea syndrome

G.E. de Vries1, P.M. Meijer2, J.H. van der Hoeven2, R.A. Feijen2, B. Stegenga2, P.I. Wijkstra1.

1Pulmonary Diseases and Tuberculosis, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands; 2Clinical Neurophysiology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands. As a conclusion, pts with RERAs should be evaluated for EDS for therapy with ptt improves daytime symptoms and is reasonably well tolerated.

P2217

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P2217

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G.E. de Vries1, P.M. Meijer2, J.H. van der Hoeven2, R.A. Feijen2, B. Stegenga2, P.I. Wijkstra1. 1Pulmonary Diseases and Tuberculosis, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands; 2Clinical Neurophysiology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands.

Introduction: In obstructive sleep apnea (OSA) collapsibility of the upper airway is increased in the supine sleeping position, resulting in an increase of apnea-hypopnea index (AHI) and severity of apneic events.

Aim: To assess whether the “tennis ball technique” (TBT) prevents positional OSAs-patients from lying on their back and whether this therapy is effective in reducing AHI, severity of events and excessive daytime sleepiness (EDS).

Methods: Thirty patients with a positional OSA at baseline (14 mild, 17 moderate, 2 severe) were treated with TBT. After at least 4 weeks a second sleep study under treatment was performed to assess differences between baseline and follow-up percentage in supine position, AHI, minimal oxygen saturation and EDS. Treatment was considered successful when AHI reduced <20% or reduced at least 50%.

Results: Supine sleeping position reduced from a median (IQR) of 33.2 (23.6-43.7)% to 6.6 (0.0-14.3)%; p<0.001. Minimal saturation improved from a median (IQR) of 86.0 (83.0-87.8)% to 90.0 (84.3-89.0)%; p=0.047. The Epworth Sleepiness Scale decreased from a mean (SD) of 11.2 (5.3) to 9.2 (5.3); p=0.002.

TBT treatment was successful in 23 of the 33 patients.

P2217

Efficacy of the “tennis ball technique” in patients with positional obstructive sleep apnea syndrome

G.E. de Vries1, P.M. Meijer2, J.H. van der Hoeven2, R.A. Feijen2, B. Stegenga2, P.I. Wijkstra1.

1Pulmonary Diseases and Tuberculosis, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands; 2Clinical Neurophysiology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands.

Introduction: In obstructive sleep apnea (OSA) collapsibility of the upper airway is increased in the supine sleeping position, resulting in an increase of apnea-hypopnea index (AHI) and severity of apneic events.

Aim: To assess whether the “tennis ball technique” (TBT) prevents positional OSAs-patients from lying on their back and whether this therapy is effective in reducing AHI, severity of events and excessive daytime sleepiness (EDS).

Methods: Thirty patients with a positional OSA at baseline (14 mild, 17 moderate, 2 severe) were treated with TBT. After at least 4 weeks a second sleep study under treatment was performed to assess differences between baseline and follow-up percentage in supine position, AHI, minimal oxygen saturation and EDS. Treatment was considered successful when AHI reduced <20% or reduced at least 50%.

Results: Supine sleeping position reduced from a median (IQR) of 33.2 (23.6-43.7)% to 6.6 (0.0-14.3)%; p<0.001. Minimal saturation improved from a median (IQR) of 86.0 (83.0-87.8)% to 90.0 (84.3-89.0)%; p=0.047. The Epworth Sleepiness Scale decreased from a mean (SD) of 11.2 (5.3) to 9.2 (5.3); p=0.002.

TBT treatment was successful in 23 of the 33 patients.

P2217

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TBT treatment was successful in 23 of the 33 patients.
Anastasia Papastefanou, Vaggelis Balafas, Nikos Kostomitsopoulos, George Matziaras, Katerina Vlami, Argiro Antaraki, Ultrasound evaluation of diaphragmatic function in obstructive sleep apnea diagnosis of OSA.

Methods: Sonomicrometry transducers were implanted in 12 awake canines. A tracheostomy was performed. Pressure was applied by closing a valve periodically for 10 sec. The diaphragmatic functions were compared: during normal airway breathing, sustained hypoxia and recovery.

Results: Pressure was predictive of collapsibility during sleep.

Conclusion: The addition of MMAA to a type 3 PM improves the accuracy in the detection of respiratory events and gives useful information. It improves Sensitivity and Negative Predictive Value, without a significant drop in Specificity and Positive Predictive Value, suggesting that it is an attractive device for the diagnosis of OSA.

P2219
Ultrasound evaluation of diaphragmatic function in obstructive sleep apnea

George Matziaras, Katerina Vlami, Argiro Antaraki, Anastasia Papastefanou, Vaggelis Balafas, Nikos Kostomitsopoulos, Sporos Papagi, Alkiviadis Kostakis, 2nd Pulmonary Department Attikon, Attikon General Hospital of the University of Athens, Athens, Chaidari, Greece; 2Center for Experimental Surgery, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Background: Little is known about diaphragm function during obstructive sleep apnea syndrome. On the other hand, ultrasound has been used to image the diaphragm functionally and to evaluate neuromuscular blockade. The aim of this study was to use ultrasound technique to evaluate and quantify diaphragm function in a rat model during sleep apnea under condition of normoxia.

Methods: Experiments were conducted in ten male adult Wistar rats weighing 350 gr, which were anaesthetized with Ketamine-Xylazine intraperitoneally. Air was breathing after the tracheostomization in a circuit with an electromagnetic valve which was closing periodically every minute for 10 sec for two hours, mimicking obstructive apnoeas. Supplemental oxygen was added to keep normal arterial saturation (SpO2>97%). Diaphragm Inspiratory Amplitude (DIA) (cm), Diaphragm Inspiratory Time (Ti) (sec), Ti/ET, Diaphragm Motion Time (DMT) (sec) and Diaphragm Resting Time (DRT) (sec) were measured from the M-mode sonographic images. Data analyzed and compared between normal breathing (time 0) and breathing after two hours of airway obstructions (time 0+2).

Results: All diaphragm measurements (DIA,Ti, DMT and DRT) from time 0 to time 0+2 were compared using the Wilcoxon signed-rank test and showed a statistically significant reduction (p<0.05) between the two time points.

Conclusions: These findings suggest that diaphragmatic function is affected acutely during obstructive sleep apnea. It is also indicated that diaphragmatic fatigue as expressed via DIA,DMT,DRT and Ti is present independently of hypoxemia after two hours of airway obstructions during sleep.

P2220
Effect of upper airway stimulation for quality of life and sleep architecture in patients with moderate-to-severe OSA

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Background: Electrical stimulation of the hypoglossal nerve can improve obstructive sleep apnea syndrome (OSAS). It is however unknown whether the stimulation affects sleep architecture and quality of life.

Methods: Inspire systems were implanted in moderate-to-severe OSA patients who failed, or were intolerant for CPAP. Sleep architecture was evaluated using lab-based polysomnography at pre-implant and post-implant, at which times Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FeSQ) were also collected. Results are presented as Mean ± SD.

Results: Twenty eight subjects were implanted. The data collection is on-going and 18 have completed month 12 visit. Both ESS and FeSQ improve significantly from the baseline to the last visit. There was a trend toward increased percent of slow wave sleep and REM sleep at the last visit post-implant, but no significant change in total sleep time, sleep efficiency, percent of slow wave sleep or REM sleep was detected.

Conclusion: Preliminary findings showed that upper airway stimulation improves quality of life without changing sleep architecture in patients with moderate-to-severe OSA.

P2221
Upper airway collapsibility evaluated by negative expiratory pressure test in severe obstructive sleep apnea

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Introduction: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular disease and could have serious consequences. Increased upper airway collapsibility is one of the main determinants of obstructive sleep apnea and its evaluation could be useful for identification.

Objective: To investigate usefulness of measurements of upper airway collapsibility by negative expiratory pressure application, as a screening test for severe OSA.

Method: 24 severe OSA and 24 normal subjects matched by body mass index referred to our sleep laboratory, underwent overnight sleep study and diurnal negative expiratory pressure test. Flow drop (ΔV) and expiratory volume in the first 0.2s (V0.2) during negative expiratory pressure application was measured.

Results: ΔV (%) and V0.2 (%) were statistically different between normal and apneic subjects. Apneic patients have greater falls of flow than normal subjects. Additionally, severely apneic patients exhaust during the first 0.2 s of negative expiratory pressure application, an average of only 11.2% of the inspired volume compared to 34.2% of normal subjects. Receiver operating characteristic analysis showed that V0.2 (%) and ΔV (%) could very accurately identify severe obstructive sleep apnea subjects (sensitivity of 95.8 and 91.7% and specificity of 95.8% and 91.7% respectively).

Conclusion: The percent expiratory volume at 0.2 s and flow drop amplitude is a highly accurate parameter to detect severe obstructive sleep apnea subjects. Pharyngeal collapsibility measurement during wakefulness using negative expiratory pressure is predictive of collapsibility during sleep.

P2222
Parasternal intercostal function during sustained hypoxia

Michael Ji, Tetsuomi Ikekami, Paul Easton. Department of Critical Care Medicine, University of Calgary, Calgary, AB, Canada

Introduction: In humans and other mammals, sustained isocapnic hypoxia for 20-60 minutes elicits a biphasic ventilatory response (roll-off), with initial peak ventilation followed by decline to a plateau. The activities of the respiratory muscles during the sustained hypoxic response are not known.

Aim: To study ventilation and actions of the chest wall muscles, specifically Parasternal Intercostal (PARA) during sustained hypoxia in awake canines.

Methods: After implantation of sonomicrometry transducers and EMG electrodes in PARA, and complete recovery, we measured airflow, oxygen saturation, end tidal CO2, moving average EMG and shortening (SHORT) of PARA, during room air ventilation (BASE), followed by 25 minutes of isocapnic hypoxia (mean 78% SpO2). The canines were awake, breathing through a nose mask. We report results 2-3 min after reaching SpO2 80% (PEAK) and final 5 min (PLATEAU) of sustained hypoxia, then room air breathing (RECOVERY).

Results: For N=7 (mean 28.9 kg, 28 days post implant), minute ventilation (Vt) and tidal volume (VT) increased significantly from BASE to PEAK, then decreased

<table>
<thead>
<tr>
<th>ESS</th>
<th>FoSQ</th>
<th>Total Sleep Time</th>
<th>Sleep Efficiency, %</th>
<th>Slow Wave Sleep, %</th>
<th>REM Sleep, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11.0±5.0</td>
<td>89.6±23.2</td>
<td>340.9±145.2</td>
<td>76.9±17.2</td>
<td>12.9±17.2</td>
</tr>
<tr>
<td>Last Visit</td>
<td>7.3±4.2</td>
<td>99.8±16.3</td>
<td>329.9±68.0</td>
<td>75.9±10.2</td>
<td>16.9±17.0</td>
</tr>
</tbody>
</table>

*p<0.05 between baseline and last visit
258. Cardiometabolic and neurocognitive changes in obstructive sleep apnoea

P2223
Structural brain changes related to disease duration in patients with asthma
Andreas von Leupoldt1,2, Stefanie Brassen2, Hans Jörg Baumann3, HansKlose3, Christian Büchel1,2, Andreas von Leupoldt 1,2, Stefanie Brassen 2, Hans Jörg Baumann 3, HansKlose 3, 1Department of Psychology, University of Hamburg, Hamburg, Germany; 2Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 3Department of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Dyspnea is the impairing, cardinal symptom patients with asthma repeatedly experience over the course of the disease. However, its accurate perception is also crucial for timely initiation of treatment. Reduced perception of dyspnea is associated with negative treatment outcome, but the underlying brain mechanisms of perceived dyspnea in patients with asthma remain poorly understood. We examined whether increasing disease duration of asthma is related to structural brain changes and studied the associations between structural brain changes and perceived dyspnea. By using magnetic resonance imaging in combination with voxel-based morphometry, gray matter volumes of the insular cortex and brainstem periaqueductal grey (PAG) were examined in fourteen patients with mild-to-moderate asthma and correlated with asthma duration and perceived affective unpleasantness of respiratory load induced dyspnea. Whereas no associations were observed for the insular cortex, longer duration of asthma was associated with increased gray matter volume in the PAG. Moreover, increased PAG gray matter volume was related to reduced ratings of dyspnea unpleasantness. The present results demonstrate that increasing disease duration is associated with increased PAG gray matter volume in patients with mild-to-moderate asthma. This structural brain change might contribute to reduced perception of dyspnea in some patients with asthma and, thus, negatively impact treatment outcome.

P2224
The impact of obstructive sleep apnea on glucose regulation and liver injury in nondiabetic men
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Objective: We explored the effect of Obstructive sleep apnea syndrome (OSAS) on glucose regulation and liver injury in nondiabetic men.

Results and methods: We included 49 non diabetic men of the OSAS patients with concomitant diseases/medications based on overnight polysomnography and blood tests. We measured fasting serum glucose, FPG, fasting insulin, FINS, C-reactive protein, CRP, liver enzymes such as alanine aminotransferase, ALT and lactate dehydrogenase, LDH and calculated new homeostasis model assessment estimates of insulin resistance (HOMA-IR), insulin sensitivity (HOMA-IS) and pancreatic beta-cell function (HOMA-2-B). HDL and triglycerides were significantly increased in patients with OSAS.

Results: Median fasting insulin level, HOMA-IR, and HOMA-IS of the severe OSAS group were significantly higher than those of the other OSAS subgroups and controls. No significant differences were observed for FPG and HOMA-2-B. CRP levels were significantly correlated with BMI, with AHI with the lowest Stp2q, with HOMA-IR and with HOMA-IS during sleep. Both levels of ALT and LDH were significantly positively correlated with insulin and HOMA-IR (r = 0.001 respectively). Significant elevations in HOMA-IR were seen during sleep in patients with OSAS.

Conclusions: We demonstrated that OSAS contributes to the development of insulin resistance and liver injury. Insulin resistance may be the key effect of OSAS on glucose regulation. Insulin resistance may be the pathophysiologic basis of liver injury in OSAS.

P2225
Effect of controlled blood pressure values in a population with obstructive sleep apnea syndrome (OSAS) and arterial hypertension (HT)
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Rationale: OSAS and HT are associated through cause-effect relationship, but few data in literature studies the effect of blood pressure (BP) control medication on OSAS.

Methods: We analysed 162 OSAS patients with treated HT, 46.9% with controlled BP (CBP), 53.1% with uncontrolled BP (UBP), and studied differences between groups regarding demographics, anthropometric data, symptoms, comorbidities, sleep study’s reports, therapy. We use SPSS (T, chi tests)ListenRead phonetically.

Results: 76 CBP patients: (22.8%) women, 54 (71.1%) men, mean age 59.1 ± 10.8 years, average apnea-hypopnea index (AHI) 49.5 ± 36.5; 86 UBP patients: (20 %) women, 66 (65%) men, mean age 55.3 ± 8.9 years, average AHI 58.1 ± 38.7. Statistically significant differences (p < 0.05) were in relation to other OSAS patients: more difficult to treat in these patients, who, according to the results of this study, would benefit more from CPAP therapy. OSAS may coexist in patients with HT controlled because of the presence of symptoms or signs and the patient, mostly young or middle-aged adult, cannot receive adequate treatment.

P2226
Severity of sleep-disordered breathing is an independent predictor of metabolic dysfunction in a population with obstructive sleep apnoea
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People with obstructive sleep apnoea syndrome (OSAS) are at increased risk of insulin resistance, dyslipidaemia, and adverse cardiovascular outcomes. However, obesity is a major confounding factor in studies examining the impact of OSAS on the development of these sequelae. It remains uncertain if sleep-disordered breathing is an independent driver of metabolic dysfunction.

We sought to assess the influence of OSAS severity on metabolic health by prospectively studying the fasting lipid & glycaemic profiles of newly diagnosed OSAS patients. Subjects were stratified according to OSAS severity, and lipid profiles were compared between groups. The relationship between OSAS severity and metabolic health was examined using a hierarchical multivariate linear regression model. The present results demonstrate that increasing disease duration is associated with increased PAG gray matter volume in patients with mild-to-moderate asthma. This structural brain change might contribute to reduced perception of dyspnea in some patients with asthma and, thus, negatively impact treatment outcome.

Conclusions: We demonstrated that OSAS contributes to the development of insulin resistance and liver injury. Insulin resistance may be the key effect of OSAS on glucose regulation. Insulin resistance may be the pathophysiologic basis of liver injury in OSAS.

P2227
Effect of CPAP treatment on endothelial function, inflammatory markers, blood pressure and glucose control in patients with OSAS with emphasis on gender differences
Athanasios Panoutopoulos1, Anastasios Kallianos1, Apostolis Pappas1, Lembonia Velentza1, Christos Mermigkas1, Koastinios Kostopoulos1, Vasileios Kouranos2, Aggeliki Rapiti3, Eleni Koufogiorga1, Alexandros Mittasakis1, Andrea Elena Malaut2, Romania; 2Ramona Liela Nedelea2, Ruxandra Ulmeana1, Ion Mieruz-Mazile1, Florin Dumitru Mihalcan1, 1Pneumology III, University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania; 2Pneumology III, Institute of Pneumology “Marius Nasta”, Bucharest, Romania; 3Pneumology III, Faculty of Medicine and Pharmacy, Oradea University, Bucharest, Romania; 4Statistical Laboratory, Technical University of Civil Engineering, Bucharest, Bucharest, Romania

Introduction: Research evidence suggests the presence of endothelial dysfunction
and systemic inflammation in patients with obstructive sleep apnea syndrome (OSA). The effects of CPAP on the aforementioned pathophysiologic pathways, as well as on the systemic disease that result or coexist with the OSA remains elusive.

Aim: To assess the effect of CPAP therapy on endothelial-dependent dilation, plasma levels of inflammatory markers, blood pressure and glucose control in male and female patients with OSA.

Methods: Our study group consisted of 40 patients with no prior history of cardiovascular disease, with an Apnea-Hypopnea Index (AHI) >15 who were assigned to receive CPAP treatment. Measurement of Flow Mediated Dilation (FMD), 24 hour ambulatory blood pressure (BP) and blood analysis were performed at baseline and 3 months after CPAP therapy.

Results: Baseline FMD values were negatively correlated the AHI (r=0.55, p=0.001). After 3 months of CPAP there was a significant increase in the FMD values and a significant reduction in the patients’ 24hr systolic BP, diastolic BP and Pulse Pressure (PP), daytime systolic and diastolic BP, nighttime systolic BP and the reactive protein (CRP) and HbA1c levels. When divided by gender only male patients produced similar statistically significant results.

Conclusion: Our results suggest that CPAP therapy improves the endothelial function, the blood pressure and glucose control in male patients with OSA.

Further research is warranted in order to further elucidate the impact of CPAP on the cardiovascular risk of male and female patients with OSA.

P2228
Endothelial function in obstructive sleep apnea syndrome
Evangelos Markozanès, Fotis Kapismalis, Kyriaki Cholidou, Konstantina Kyrkou, Konstantina Kosta, Manos Alchanatis. 1st Respiratory Medicine Department, Sotiria Hospital, University of Athens, Athens, Greece

Introduction: Obstructive sleep apnea (OSA) is an independent risk factor for myocardial infarction and stroke. Endothelial dysfunction could be one of the pathogenetic mechanisms linked to OSA related risk for cardiovascular diseases.

Aim: To assess the effect of CPAP on endothelial markers and serum inflammatory cytokines in OSA patients.

Methods: We studied 38 patients by polysomnography in the laboratory, 27-86 years (1.55 ± 0.3 vs. 1.76 ± 0.2, p=0.02) and higher minimal SaO2 (80.3% ± 9.1% vs. 87.4% ± 9.1%, p=0.02). They were slightly older (51.9 ± 7.2 years vs. 43.4 ± 7.3 years, p>0.05) and higher BMI (33.1 (7.1) vs. 28.7 (5.7), p<0.01). Baseline hsCRP (mg/dl) was higher in male patients (0.44 (0.5) vs. 0.36 (0.75), p=0.008, beta=-0.450, R2 =0.23, p=0.008).

Conclusion: The results of our study confirm the effects of CPAP therapy on endothelial markers and serum inflammatory cytokines. Further studies are needed to confirm these findings.

P2229
The lack of evidence based knowledge of metabolic syndrome in obesity hyperventilation syndrome
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Introduction: The obesity hyperventilation syndrome (OHS) is a severe sleep related breathing disorder, with obstructive sleep apnea syndrome (OSAS) as the predominant sleeping pattern. It is often accompanied by multiple organ tract involvement. In OAS, the interaction with metabolic syndrome is well studied. In OHS however, it is unclear whether the severity of disease has consequences for the occurrence and severity of metabolic syndrome. We evaluated the presence of evidence based knowledge.

Methods: A systematic Pubmed and Cochrane search was performed, final check 24th February 2011, for metabolic syndrome in concurrence with OAS and OHS, and related terms and synonyms in title and abstract (exclusion criterion: duplicates). The final data set was achieved by elimination of studies that conformed predefined criteria: animal studies, studies < 1990, age < 18 years, genetic diseases, case reports, and studies without original data. Outcome parameters were total number of studies and randomized controlled trials (RCT), before and after the elimination strategy, for OSA and OHS versus OSA.

Results: 767 initial hits were found in OSA, versus 273 for OHS. After the predefined elimination strategy, 171 remained, containing 5 RCT’s for OSA, versus 6 studies, without any RCT, for OHS (Fischer exact p < 0.0001 for final total number and p < 0.05 for RCT’s).

Conclusion: A markedly lower number of hits was found for metabolic syndrome in OHS, as compared to OSA. Within the complexity of clinical features in OHS, the metabolic syndrome seems to be an unexplored area in research.

P2320
C-reactive protein (CRP) levels in obstructive sleep apnea (OSA) patients and relation to severity of OSA
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Introduction: CRP has been proposed as a cardiovascular risk marker. OSA is associated to metabolic syndrome and major cardiovascular events.

Objectives: To study CRP levels in OSA patients in comparison to healthy people, and the relationship between severity of OSA and CRP levels.

Method: Case-control study including 100 consecutive diagnosed OSA patients and 113 healthy people randomly selected from general population. Age, sex, hypertension, diabetes, diabetes, body mass index (BMI), smoking, Epworth scale, spirometry, respiratory disturbance index (RDI) and high sensitivity CRP (hsCRP) were measured.

Results: Cases and controls characteristics are shown in Table 1. Multiple regression model analysis coefficients of CRP levels in OSA patients are shown in Table 2.

Table 1. Case and control characteristics
OSA patients Healthy people P value

Age (years) [mean (standard deviation)] 54 (13.7) 49 (14.8) 0.01
Male (%) 71 52 0.003
BMI (kg/m²) 33.1 (7.1) 28.7 (5.7) <0.01
Hypertension (%) 37 28 0.174
Diabetes (%) 22 10 0.02
Hyperlipidemia (%) 39 34.5 0.46
Smoker or ex-smoker (%) 51 34.5 0.015
hsCRP (mg/dl) 0.47 (0.75) 0.44 (0.75) 0.002

Multiple regression model analysis coefficients of CRP levels in OSA patients are shown in Table 2.

Table 2. Multiple linear regression model coefficients for hsCRP levels in OSA patients

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.03</td>
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<tr>
<td>BMI</td>
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<tr>
<td>BMI</td>
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<tr>
<td>BMI</td>
<td>0.69</td>
</tr>
<tr>
<td>BMI</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Table 3. Interaction variable

Conclusion: Although OSA patients shows slightly higher levels of hsCRP than healthy people in our sample, other factors rather than severity of OSA measured by the RDI influence that issue.

P2331
Efficacy of BiPAP AutoSV advanced in subjects with congestive heart failure and central apnea
Winfried J. Randerath1, D. Banerjee1, M. Treml1, W. Galecke1, C. Priezagl2, A. Ali3, S. Taheri1. 1Institut für Pneumologie, Krankenhaus Bethanien gGmbH, Solingen, Germany; 2Department of Respiratory Medicine; Birmingham Heartland Hospital, Birmingham, United Kingdom

Introduction: Auto-Servo Ventilation effectively suppresses Sleep Disordered Breathing (SDB) in patients with Congestive Heart Failure (CHF). This study compared the efficacy of a new mode of ASV that incorporates an automatic EPAP (ASV-Advanced), with and without its Bi-Flex comfort feature, to manually titrated ASV (ASV) in patients with central SDB and CHF.

Methods: Following diagnostic PSG and titration, patients underwent 3 consecutive treatment nights in a random order: ASV, ASV-Advanced and ASV-Advanced with Bi-Flex. For the ASV night, EPAP was set to the level determined during the titration night and Bi-Flex at EPAP+2cmH2O. For the ASV-Advanced nights, the

Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ASV3 Bi-Flex</th>
<th>ASV3</th>
<th>ASV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI (h)</td>
<td>41.6±14.5</td>
<td>73.3±2.4</td>
<td>70.8±8.8</td>
</tr>
<tr>
<td>AHI REM (h)</td>
<td>19.3±10.1</td>
<td>6.9±13.3</td>
<td>6.0±10.7</td>
</tr>
<tr>
<td>AHI NREM (h)</td>
<td>44.3±19.5</td>
<td>7.5±6.8</td>
<td>7.9±9.2</td>
</tr>
<tr>
<td>cAI (h)</td>
<td>16.8±16.0</td>
<td>0.6±9.0</td>
<td>0.6±9.0</td>
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<tr>
<td>HI (h)</td>
<td>15.8±13.0</td>
<td>6.5±6.6</td>
<td>5.7±2.5</td>
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<tr>
<td>CSRI (h)</td>
<td>23.7±16.0</td>
<td>0.9±2.4</td>
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<tr>
<td>RAI (h)</td>
<td>18.6±12.2</td>
<td>3.5±5.9</td>
<td>3.7±6.0</td>
</tr>
</tbody>
</table>

RDI, Respiratory Disturbance Index; AHI, Apnea-Hypopnea Index; cAI, Central Apnea Index; HI, Hypopnea Index; CSRI, Chuyen Noks Respiratory Index; RAI, Respiratory Arousal Index. *p<0.001 vs. diagnosis
device was set to automatically determine EPAP and IPAP pressures with a maximum pressure support of 20cmH2O. When activated, Bi-Flex was set to its maximum expiratory pressure relief. Data were analyzed with ANOVA and Bonferroni.

Results: Ten males participated (mean ± SD: age 67.4±11.7, BMI 28.4±4.5 kg/m2, LVEF 25.7±5.7%). Sleep time and efficiency were similar.

Conclusion: ASV-Advanced treats central SDB as effectively as ASV in patients with CHF.

P2232 Metabolic and inflammatory profile in obese and non obese children with obstructive breathing disorders
Silke Weber1, Érico Moreira 1, Renata Mizusaki Iyomasa 1, Ana Carolina Silveira 1, Cinthya Kurokawa 2, Otolaryngology, Pediatrics, Botucatu Medical School São Paulo State University, Botucatu, São Paulo, Brazil

Introduction: Adult OSA is a known risk factor for metabolic diseases, but still unexplored in children. Obesity, an important cofactor, is increasing in the pediatric population.

Aim: Study the metabolic profile and the levels of TNF-α in obese and non obese children with obstructive breathing disorders.

Methods: Children of both genders, aged 6 to12 years, with obstructive breathing disorders were included. Children were divided in 2 groups, obese and non obese, where blood samples were taken for analysis. The lipids, glucose, insulin, tyroxin and TNF-α levels were determined. Results were compared for the 2 groups.

Results: 17 children, median age of 6.5 years, 10 obese- and 7 non obese, were included. There glucose level was 85 mg/dl in both groups. Insulin level was higher in the obese group (10.7±2.3 mU/L, X 6.7±3.29 mU/L, p<0.01). There were no significant differences in total cholesterol (108±4.37 mg/dl vs 181±5.33, p<0.05), HDL (56±1.45 mg/dl vs 49±1.78 mg/dl, p<0.05) and LDL (98±22.7 mg/dl vs 110±7.28 mg/dl) in the non obese and obese group, respectively. TGL levels were higher in the obese group (106.5±37 mg/dl vs 64±23 mg/dl). Thyroxin and TSH levels did not differ in both groups. The average TNF-α was 0.36±0.09 pg/ml but differed in obese 0.56±0.53 pg/ml and 0.10±0.07 pg/ml (p<0.05).

Conclusion: Obesity may cause additional metabolic changes (increased insulin resistance and TGL levels) in children with obstructive breathing disorders. The metabolic inflammatory profile must be investigated for a better understanding of OBD in childhood.

P2233 Cognition, quality of life and adherence to CPAP after 18-months treatment in obstructive sleep apnea patients
Vincenzo Castronovo1, Sara Marel1, Mark S. Aloia2, Marco Zucconi 1, Silke Weber1, Érico Moreira 1, Ana Carolina Silveira 1, Cinthya Kurokawa 2, Otalaryngology, Pediatrics, Botucatu Medical School São Paulo State University, Botucatu, São Paulo, Brazil

Obstructive Sleep Apnea (OSA) determines cognitive dysfunctions and diminished quality of life (QoL). Adherence to CPAP treatment although effective, still remains a challenge for patients.

Aims: To evaluate neurocognitive functions, adherence to PAP and QoL in a consecutive group of OSA patients at baseline (BL) compared to age and education-matched normal controls and to assess changes after 18-months of fixed PAP treatment (FU) with C-flex (Philips/Respironics).

Methods: 10 patients were excluded for low compliance to PAP within the 18-month observation period. At BL patients showed significantly lower scores than controls in all neurocognitive domains (p<0.05) as well as in FOSQ (p<0.001) and SF36. At FU an overall significant improvement in the general health subscale of SF36. At FU mean compliance to PAP was 6.1±1.36 hrs and% of days of use 88.5±11.7. There glucose level was 85 mg/dL in both groups. Insulin level was higher in the obese group (10.7±2.3 mL, X 6.7±3.29 mL, p<0.01). There were no significant differences in total cholesterol (108±4.37 mg/dl vs 181±5.33, p<0.05), HDL (56±1.45 mg/dl vs 49±1.78 mg/dl, p<0.05) and LDL (98±22.7 mg/dl vs 110±7.28 mg/dl) in the non obese and obese group, respectively. TGL levels were higher in the obese group (106.5±37 mg/dl vs 64±23 mg/dl). Thyroxin and TSH levels did not differ in both groups. The average TNF-α was 0.36±0.09 pg/ml but differed in obese 0.56±0.53 pg/ml and 0.10±0.07 pg/ml (p<0.05).

Conclusion: Obesity may cause additional metabolic changes (increased insulin resistance and TGL levels) in children with obstructive breathing disorders. The metabolic inflammatory profile must be investigated for a better understanding of OBD in childhood.

P2234 Association between arterial hypertension and impaired glucose tolerance (IGT) in obstructive sleep apnea (OSA) patients
Robert Pływaczewski1, Przemysław Bielen1, Luiza Jonczak 1, Dorota Gorecka 2, Robert Pływaczewski1, Przemyslaw Bielen1, Luiza Jonczak 1, Dorota Gorecka 2, Robert Plywaczewski1, Przemyslaw Bielen1, Luiza Jonczak 1, Dorota Gorecka 2, Robert Plywaczewski1, Przemyslaw Bielen1, Luiza Jonczak 1, Dorota Gorecka 2, Robert Pływaczewski1, Przemyslaw Bielen1, Luiza Jonczak 1, Dorota Gorecka 2

Obstructive sleep apnea is a risk factor of cardiovascular and metabolic disturbances. The aim of this study was to assess relationship between IGT and AHI, obesity and cardiovascular diseases in OSA subjects. We studied 255 OSA pts (195 males (76.5%) and 60 females (23.5%), mean age – 56 ±8.10.7 years. AHI > 5±20.3. BMI – 33±5.5 kg/m2, S02 – 91.7±4.7%, T90-19±1.25±4.8%.

Impaired glucose tolerance (IGT) (plasma level ≥ 140 mg% after 2 hours of administration 75 g glucose in oral glucose tolerance test (OGTT)) was found in 69 subjects (27.1%). In 11 patients (4.3%) OGTT confirmed diabetes (glucose ≥ 200 mg%).

Discussion: We could show, that in OSA patients during a short period of sleep the changes of BP are not directly correlated with the expected sleep or respiratory parameters but with the variation of blood pressure values. The relevance of this result for the development of hypertension remains to be proven.

This work was supported by the Fundação para a Ciência e a Tecnologia PPRO/ 82991/2007
P2236
Perception of problems driving and driving simulator performance in obstructive sleep apnoea syndrome (OSAS)
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Introduction: Advising patients with OSAS about driving is difficult. In the absence of an objective test reliance has to be given to a patient’s account of their driving ability. In simulated driving, OSAS patients perform worse than controls but an individual’s performance does not correlate with severity or symptoms of OSAS. Patients’ account is also likely to be influenced by worry of losing licence. The relationship between patients’ perception & driving simulator performance was explored as part of development of an advanced office based driving simulator (Mobile360) for pre-operative OSAS assessment.

Methods: 72 patients (ESS 12±6.0, ODI 39±2.21) completed a questionnaire pertaining to their driving behaviour & completed 50 minutes of simulated motorway driving. Two events were programmed that required evasive action to avoid a crash: minor & major. A “fail” was defined by an unprovoked crash or crash at the minor event. A crash at the major event was deemed as “indeterminate”, the rest were deemed to have “passed”. Chi squared test was performed to see whether patients admitted to problem driving were more likely to “fail” Logistic regression analysis was performed to predict a “fail” from the questionnaire.

Results: 54% subjects admitted to problem driving. Only the ESS was higher in these patients (p<0.001). A “fail” could not be predicted from the questionnaire. Subjects who reported problem driving were not significantly more likely to fail than others. This highlights that patients’ perceptions are not a reliable indicator of driving ability in OSAS. An objective test that is reliable, repeatable and practical for everyday clinical use is needed to inform decision making.

P2237
Effects of non-surgical therapeutic program on the metabolic syndrome (MetS) in morbidly obese patients
Miodrag Vukcevic1, Milina Tancic2, Svetlana Vujovic2. 1Pulmonary Department, KBC B Kosa, University Medical School, Belgrade, Serbia; 2Clinic of Endocrinology, Clinical Center of Serbia, University Medical School, Belgrade, Serbia

Objective: The aim of this study was to assess the effects of non-surgical therapeutic program on the metabolic syndrome (MetS) in morbidly obese patients.

Methods: Sixty-four extremely obese patients were involved in the therapeutic program, which consisted of two alternating phases: the three-week therapeutic fasting or semi-fasting in hospital conditions and the low caloric diet (LCD) with dosed physical activity in outpatient conditions. At the baseline we measured: anthropometric parameters, blood pressure and lipid profile. Subjects underwent an oral glucose tolerance test (OGTT) and insulin resistance/sensitivity was evaluated by the homeostasis model assessment (HOMA) and the oral glucose insulin sensitivity (OGIS). After weight reduction by at least 10%, all mentioned assessments were repeated.

Results: None of the patients had significant adverse effects. Forty-one patients aged 43±11 completed the study. The mean weight loss was 27 kg or 18% of the initial weight (p<0.01), which was followed by a significant decrease of the insulin resistance, the overall prevalence of MetS (32%) and all MetS parameters, without the significant change in high-density lipoprotein (HDL). In the subgroup of 15 patients weight reduction of 20% of the initial weight (p<0.01) resulted in AHI reduction of 31%.

Conclusions: This weight loss program substantially improves the MetS in extremely obese patients. The tailored alternating either fasting or semi fasting should be considered as an optional approach to manage extreme obesity and related metabolic adverse effects and reduce severity of sleep breathing disorders.

P2238
A study of insulin resistance in moderate to severe obstructive sleep apnea in non diabetics and its response to nasal CPAP treatment
Archanas Babu Rao, George Albert D. Souza, Striram Sampath, Uma Subramanian Unni. Chest Diseases, Critical Care, St Johns Medical College Hospital, Bangalore, Karnataka, India

Background: The effects of nasal continuous positive airway pressure (nCPAP) for obstructive sleep apnea (OSA) on insulin resistance (IR) are not clear and have found conflicting results.

Aims and objectives: To evaluate IR in non diabetic patients with moderate to severe OSA and its response to treatment with nCPAP on IR in these patients.

Method: 30 consecutively newly diagnosed patients with moderate to severe OSA were enrolled in the study. Samples of peripheral venous blood for measurement of glucose and insulin were collected after overnight fasting and IR was calculated by HOMA (Homeostasis model assessment) method. Patients were treated with nCPAP for 1month and HOMA IR was again measured.

Results: 30 OSA subjects, with a mean apnea-hypopnoea index (AHI) of 80.46 [57.24] were included in the study. The HOMA IR (5.78) was significantly higher compared to normal south indian population. There was no positive correlation of HOMA IR with AHI. This may be due to the small sample size and IR attributable to OSA may be small and constant and not related to the severity. The HOMA IR was measured 1 month after use of CPAP. The HOMA IR significantly improved from 5.78 to 4.82 (p=0.024) after 1 month of treatment with nCPAP in OSA patients. There was also significant improvement in insulin levels from 21.75 to 19.39 (p=0.009).

P2239
Relationships between obstructive sleep apnea and antioxidant/antioxidant status
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Introduction: In Sleep Apnea Syndrome (SAS) the episodes of hypoxia/reoxygenation can generate reactive oxygen species and promote oxidative stress.

Aim of the study: Evaluation of possible relationships between obstructive sleep apnea and biomarkers of oxidative stress in patients with SAS.

Methods: Two Romanian groups, consisting of 29 patients diagnosed with SAS and 17 healthy controls, were recruited. All subjects underwent cardiorespiratory polypigraphy. Plasma levels of homocysteine (Hcy), glutathione reductase (GSSG-Red), glutathione peroxidase, endothelin-1, low density lipoprotein (LDL), high density lipoprotein (HDL) and uric acid were assessed. Statistical analysis was performed using Spearman and Pearson correlations tests, two tailed test and one-way ANOVA test.

Results: The mean values of LDL were statistically significant higher in SAS patients (p=0.05), while GSSG-Red was higher in controls (p=0.01). In SAS group, correlations were found as follows: GSSG-Red and snoring (r=0.34; p=0.05); GSSG-Red and apneas number (r= -0.36; p=0.05); body mass index (BMI) and uric acid (r=0.43; p=0.01), ratio Hcy/BMI and HDL (r=0.52; p=0.003).

Conclusions: Plasma GSSG-Red and Hcy levels may be used as possible markers to provide information related to oxidative/antioxidant status in SAS patients, making them more prone to developing proatherosclerotic disease.

P2240
Road traffic collisions caused by sleepiness in UAE
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Introduction: Road traffic collision RTC is a major health problem in UAE. Sleep as a contributing factor to RTC is not well-studied in the Middle East.

Objective: We aimed to study the proportion of RTC caused by sleep behind the wheel and the factors contributing to sleep related collisions SRC.

Methods: All data of hospitalized drivers who were involved in RTC in Al-Ain city were prospectively collected during the period of April 2006-October 2007. Variables studied included, driver’s demographic data, time, date, location, mechanism of collision, speed at collision and whether sleepiness was a contributing factor reported by the drivers. A direct logistic regression model was performed to define factors related to sleep while driving.

Results: 444 drivers (92% males) were involved in RTC’s during the study period. Sleepiness of drivers was a contributing factor in 5%. Most of the drivers with SRC (79%) reported to speed 100 Km/hr or more during the collision. Rollover was the most frequent mechanism of SRC (58%). SRC was strongly over-represented during Ramadan (79%), in drivers aged 19-35 (84%) and in drivers with sleeplessness (91%).

Conclusions: Sleep disturbance is a major factor in RTC occurrence in UAE. The prevention of sleepiness and awareness of the potential consequences of driving while sleepy should be emphasized. A ‘sleepy driving detection system’ may help to reduce the number of RTCs that are due to sleepiness.

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259. Comorbid obstructive sleep apnoea (OSA) and OSA comorbidities

P2243
Does respiratory irregularity contribute to the pathogenesis of sleep-disordered breathing in multiple system atrophy?
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Background: Multiple system atrophy (MSA) is the neurodegenerative disease characterized by autonomic failure, parkinsonism, and cerebellar ataxia in various combinations, and has high frequency of sleep-disordered breathing (SDB), which caused by dysregulation of respiratory control.

Aims: This study investigates whether respiratory irregularity is involved in the development of SDB with MSA.

Methods: 22 MSA patients (9men, 60±6.2 years, BMI 23.1±5.0 kg/m²) were enrolled from January 2007 to June 2010. We performed polysomnography (PSG) and laryngoscopy under propofol sedation. Respiratory irregularity was assessed by approximate entropy (ApEn) of respiratory movement, which is a measure of system complexity (Pincus SM, Proc. Natl Acad. Sci. USA 1991). We evaluated from the two-minute data of respiratory movement before falling asleep in PSG (Burioka N, et al. Chest 2003). We chose the age-, sex-, and apnea-hypopnea index (AHI)-matched controls from ordinary obstructive sleep apnea (OSA) patients (BMI 27.6±4.5 kg/m²).

Results: PSG demonstrated that all MSA patients fulfilled OSA criteria, and their AHI was 40±6.26 per hour. Laryngoscopy showed that 15 patients (68%) had vocal cord abductor paralysis (VCAP). In the MSA group, there was a significant correlation between AHI and ApEn of respiratory movement (r=0.63, p<0.01). However, AHI had no correlation with age, BMI, duration and severity of MSA, degree of VCAP, and any respiratory parameters. In the control group, their AHI significantly correlated with BMI (r=0.68, p<0.01), but not with ApEn.

Conclusions: This study raises the possibility that respiratory irregularity influence the severity of SDB in MSA.

P2244
The relationship between obstructive sleep sleep apnoea syndrome and apolipoprotein E alleles
Ebru Kucak1, Oner Balbay2, Ali Nihat Annakaya1, Ege Gu dic Balbay2, Fatma Sifan1, Peri Arab1, 1Chest Diseases, Duzce University Faculty of Medicine, Duzce, Turkey; 2Chest Diseases, Duzce Ataturk State Hospital, Duzce, Turkey

Aim: Clinical and epidemiological studies indicate that OSA has a strong genetic basis. Apo E in humans is an important determinant of blood lipid levels. There are few studies investigating the possible relationship between Apo E and OSA. In this study, we aimed to investigate the association of Apo E alleles with OSA.

Method: 62 adult patients (35 male, 27 female) with sleep apnea applying to Chest Diseases Clinic between October 2006 and May 2009 were included in this study. All patients underwent fullnight PSG and were evaluated for apolipoprotein E alleles.

Results: The mean age was 51±12. According to PSG results, 20 cases with negative PSG and 18 with mild, 10 with moderate, 14 with severe OSA patients was diagnosed. Genetically important patients were divided into 2 groups according to AHI<15 (n:38) and AHI>15 (n:24). No homoygote Apo E2 (22) and homoygote Apo E4 (44) were observed in study group. The cases with OSA had almost statistically significant higher Apo E2 frequency than that of not OSA (23.8%, respectively, p=0.02). Apo E3 allele was significantly correlated with BMI (r=0.40, p=0.003). There was no significant correlation between AHI and Apo E2 frequency.

Conclusions: The presence of Apo E2 allele is a risk factor for OSA. Further studies are needed to confirm this relation.

P2245
A case of obstructive sleep apnoea syndrome with bilateral vocal cord paralysis
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Aim: Bilateral vocal cord paralysis (BVC) often caused by trauma, is a rare, but life-threatening condition in patients. Although the most common symptom seen in BVC is respiratory distress, hoarseness and the symptoms of sleep apnea are rare. Here we present an interesting and educative case of BVC, caused obstructive sleep apnea syndrome (OSAS).

Results: A 46- year-old male patient who had a history of snoring, apnea, excessive daytime sleepiness (EDS), admitted to our outpatient clinic with complaints of dypnea and hoarseness. He had these symptoms for a year, but progressed during the last two months. He had also a history of diabetes mellitus and COPD

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for a year, smoked 25 pack-years. Full-night polysomnography revealed that his apnea-hypopnea index was 67.7/h and minimal oxygen saturation level was 75%, diagnosed as severe OSA. His pulmonary function test demonstrated variable extrathoracic airway obstruction. The ear-nose-throat consultation revealed that vocal cords were bilaterally paralytic at the median border. His chest film, Thorax CT and neck CT were normal. The histopathological examination of biopsies from subglottic region and left vocal cord was reported as edema, hyperemia and chronic inflammation. The patient did not benefit from CPAP titration and the tracheostomy was opened due to the progression of respiratory distress. Later, right arytenoidectomy was performed. The patient indicated that snoring, EDS, hoarseness and dyspnea were improved after the operation.

Conclusion: BVP rarely causes OSA. Thus, a multidisciplinary approach in the diagnosis and treatment of these cases should be done urgently to have a better survival.

P2246
Comorbidities of obstructive sleep apnoea syndrome
Madhav Tamhankar, Murali Mohan, Ranganath Ramanjaneya, Tyas Sen.

Introduction: Obstructive Sleep Apnoea (OSA) is often associated with unrecognized comorbidities. Persons of South Asian origin already have a higher prevalence of diabetes and hypertension than in the developed world, and COPD prevalence is rising fast. We expected that the prevalence of comorbidities would be high in our population with OSA.

Methods: Patients at our referral hospital in India, proven by polysomnography to have moderate to severe OSA (Apnoea Hypopnea Index (AHI) >15/hour), were studied for important comorbidities: diabetes mellitus (DM), hypertension (HTN) and COPD diagnosis as per accepted guidelines (ADA, NICE, VII, GOLD), or already on treatment. Results were compared with recent Indian prevalence data for these comorbidities.

Results: Moderate to severe OSA was present in 182/201 subjects (90.54%) and severe OSA in 169/201 subjects (84.08%). (Age: Mean 55.65 years Range 27 – 78 years). [(Gender: Men 138 (67.6%) Women 63 (31.3%)]. The comorbidities were:

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>46.7</td>
</tr>
<tr>
<td>HTN</td>
<td>58.8</td>
</tr>
<tr>
<td>DM + HTN</td>
<td>35.7</td>
</tr>
<tr>
<td>COPD</td>
<td>25.3</td>
</tr>
</tbody>
</table>

127/182 (69.8%) of those with moderate to severe OSA had both DM and HTN. All comorbidities exist at a much higher level in persons with moderate to severe OSA than in the general population (estimated prevalence: DM 9%, HTN 28%, COPD 25%). Prevalence of DM, HTN, and COPD diagnosis as per accepted guidelines (ADA, NICE, VII, GOLD), or already on treatment.

Conclusion: Moderate to severe OSA is associated with a high prevalence of significant comorbidities like diabetes, hypertension and COPD. The prevalence is higher than a chance co-occurrence of common conditions in the general population. A search for OSA should be made in every patient with DM, HTN or COPD and vice versa.

P2247
Sleep apnoea in patients with renal transplantation
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Sleep apnoea is an important risk factor for cardiovascular mortality. With up to 50%, cardiovascular events are the major cause of death in patients with end stage renal disease (ESRD). Moreover, major adverse cardiac events (MACE) often limit the long term survival after successful kidney transplantation. Therefore a consequent detection and reduction of cardiovascular risk factor should be a major goal in patients with ESRD in particular for patients on the waiting list. Sleep apnoea (SA) has a prevalence of 30-80% in dialysis patients. The diagnosis of SA is difficult in patients with ESRD since conventional questionnaires are often misleading.

We started a study to investigate the prevalence of sleep apnoea in patients with renal transplantation. The study collective includes over 130 patients, more than 50 of them received a living transplantation. The prevalence of sleep apnoea in our study group was round about 40%. There was no influence of the typical risk factors for sleep apnoea such gender and BMI in our patient collective. The age (P=0.003) and the co-existence of other cardiovascular diseases (p<0.001) were the most important risk factors for sleep apnoea. Also typical diastolic parameters like diuresis and time on dialysis influences the appearance of sleep apnoea. Notably symptomatic like sleepiness and snoring or the Epworth Sleepiness Scale were not usefull to detect sleep apnoea in our study collective.

The study will be finished in summer 2011. Further study datas will be expected. For conclusion we can summarize that it is very useful to screen everybody on the waiting list for kidney transplantation because it presents a very common cardiovascular risk factor in patients with renal disease.

P2248
Sleep related disorder of breathing in syndromic and non syndromic craniosynostosis
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Aims: To look at sleep related disorders breathing (SRDB) in syndromic (SC) & non-syndromic craniosynostosis[NSC] children in our hospital.


Methods: Children with no SRDB history (Group1-SC, n=40) & (Group2-NSC, n=10) were referred for polysomnography (PSG) between Sep2007 to Nov2010 prospectively.

Results: The median total apnea-hypopnea index (TAHI) were 8.80 (range 1.8-18.2), 2.8 (range 0.2-21.4) & central apnea index (CAI) were 0.6 (range 0.2-2), 0.1 (range 0.1-2.1) group-1 & group-2, respectively.

<table>
<thead>
<tr>
<th>No</th>
<th>Age at PSG (in years)</th>
<th>Sex</th>
<th>TAHI (Events/Hour)</th>
<th>CAI (Events/Hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.79 Male</td>
<td></td>
<td>18.2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.85 Female</td>
<td></td>
<td>7.4</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>1.52 Male</td>
<td></td>
<td>1.8</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>8.78 Female</td>
<td></td>
<td>9.2</td>
<td>0</td>
</tr>
</tbody>
</table>

P0,003

PSG: Polysomnograph, TAHI: Total Apnoea Hypopnoea Index, C0AI: Total Central Apnoea Index.

Conclusion: Asymptomatic SC & NSC children have PSG evidence of SRDB.

References:

P2249
Should cardiologists routinely screen and evaluate myocardial infarction patients for sleep disorders?
Filip M. Szymanski1, Krzysztof Filipiak1, Anna Hryniewicz-Szymanska2, Grzegorz Karpinski1, Grzegorz Opolch1. 1Department of Cardiology, The Medical University of Warsaw, Warsaw, Poland; 2Department of Cardiology, Hypertension and Internal Diseases, The Medical University of Warsaw, Warsaw, Poland

Introduction: A risk of a cardiovascular event increases with the number of cardiovascular risk factors.

Aims: The aim of this prospective study was: To identify Acute Coronary Syndrome (ACS) patients at high risk of OSA, using Berlin questionnaire (BQ) and Epworth Sleepiness Scale (ESS), and 2. To decrypt the clinical characteristics of ACS patients at high risk of OSA.

Methods: We studied 158 consecutive patients, assessed by BQ and the ESS. The high risk of OSA was defined as cumulative high risk, based on BQ and ESS scores higher than 10 in a scale of 24.

Results: Fifty four (34.2%) patients were at high risk. On admission patients at high risk of OSA had significantly often history of hypertension (92.6% vs. 26%; p=0.001), diabetes mellitus (37% vs. 15.4%; p=0.0049), significantly higher mean ESS (14.83±3.02 vs. 5.83±3.33; p=0.00049), systolic blood pressure (139.4±4.34±2 vs. 128.4±23.6 mmHg; p<0.0001), diastolic blood pressure (87.7±17.4 vs. 76.2±12.1 mmHg; p<0.0001), Body Mass Index (32.3±4.6 vs. 27.3±8 kg/m2; p<0.0001), and lower Glomerular Filtration Rate (79.5±21.2 vs. 87.5±22.2 ml/min/1.73 m2; p=0.048). Patients at high risk of OSA had often onset of acute chest pain between midnight and 5.59 am compared to the patients at low risk (42.6% vs. 26%; p<0.05). Mortality (7.4% vs. 1%; p=0.03) was more frequent in patients at high risk of OSA.

Conclusions: Every third ACS patient was diagnosed with OSA. Cardiologists should routinely screen and evaluate myocardial infarction patients for sleep disorders, especially when they are obese, have hypertension, and chest pain in the night hours.
P2250
Daytime sleepiness in patients on intrathecal chronic opioid (IT) therapy is not related to sleep disordered breathing (SDB)
Francescca Carriquiry Iglesias1, Maria Paige2, Paola Penna3, Michelangelo Buonomore1, Massimo Barbieri2, Cesare Bonetti2, Silvia Dumitru1, Chest Center, S. Maugeri Foundation Institute of Pavia, Pavia, Italy; 4Neuropsychological Unit, S. Maugeri Foundation of Pavia, Pavia, Italy.

Aim of our study was to study two groups of consecutive patients receiving IT opioid therapy, according to absence (A, noS) or presence (P, n=5) of EDS. All the patients (18 F, age 56.9±8.3 yrs, BMI 25.6±6.6 kg/m²) underwent polysomnography (PSG) and maintenance wakefulness test (MWT). Table 1 shows sleep indices for both group of patients:

<table>
<thead>
<tr>
<th>SE (%)</th>
<th>N2 (%)</th>
<th>N1 (%)</th>
<th>REM (%)</th>
<th>AH1</th>
<th>ODI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>28.6±1.3</td>
<td>32.9±1.65</td>
<td>20.9±6.6</td>
<td>18.8±1.3</td>
<td>10.4±7.8</td>
</tr>
<tr>
<td>P</td>
<td>30±14.3</td>
<td>52.9±16</td>
<td>14.1±2.9</td>
<td>17.3±6.4</td>
<td>23.8±30</td>
</tr>
<tr>
<td>AHI</td>
<td>8±14</td>
<td>41.9±18</td>
<td>22±16.7</td>
<td>16.7±7</td>
<td>21.5±23</td>
</tr>
<tr>
<td>*p&lt;0.05</td>
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Both EDS and sleep latency at MWT were statistically significantly correlated with BMI (Pearson r=0.04; p=0.06). The 6 patients were affected by sleep apnea (AH1 32.8±26): central in 1, mixed in 1 and obstructive in 4 patients. Age was statistically significantly correlated with AH1 (r=0.96, p<0.01) and ODI (r=0.62, p<0.05). No statistically significant correlation were found between respiratory and sleepiness indices as well as morphine equivalent doses or years of opioid therapy. In conclusion, daytime sleepiness is common in patients receiving IT opioids but it is only correlated with sleep quality and not with respiratory disturbances.

P2251
Obstructive sleep apnea syndrome in patients with primary open angle glaucoma
Ege Gulce Balbay1, Oner Balbay2, Mural Tunç3, Harun Yüksel4, Ali Nihat Annakkaya2, Per Arzb5, Talha Dumlup6, Chest Diseases, Duzce Antarkt State Hospital, Duzce, Turkey; 7Chest Diseases, Duzce University, Duzce, Turkey; 8Ophthalmology, Duzce University, Duzce, Turkey. Introduction: It was claimed that obstructive sleep apnea syndrome (OSAS) aggravates or causes glaucoma by impaired optic nerve head blood flow or by directly damage to the optic nerve secondary to prolonged hypoxia. The objective of this study was to investigate the prevalence of OSAS in patient with primary open angle glaucoma (POAG).

Material and methods: The consecutive 21 POAG patients (12 female/ 9 male) attending the outpatient clinic of the department of Ophthalmology between July 2007 and February 2008 were included in all of these patients underwent to Polysomnographic examination.

Results: The prevalence of OSAS was 33.3% in glaucoma patients (14.3% mild and 19% moderate). The age and the diameter of the neck in patients with OSAS were significantly greater than those with no OSAS. The adipose tissue thickness in triceps reached near significance in glaucomatous OSAS patients. Snoring was observed in all glaucoma cases with OSAS. Particularly, the prevalence of OSAS was significantly more common in glaucoma patients having the symptoms of habitual snoring, witnessed apnea than those of not. The prevalence of OSAS was often significantly increased with having major symptoms together.

Conclusions: Although it was not provided an evidence for a cause-effect relationship in the present study, the high prevalence of OSAS in patients with POAG might put forward a different view of aspect to ophthalmologists. Further studies are required especially in large groups who had CPAP (Continuous positive airway pressure) therapy to explore the long term results of coincidence, relation and cross interaction of these two common disorders.

P2254
Sleep disorders in morbid obesity who undergo bariatric surgery
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Introduction Insomnia and obstructive sleep apnea (OSA) often have been considered conflicting medical conditions, recent studies suggest that these two entities are often coexist.

Aims: To determine the prevalence of sleepiness and insomnia in morbidly obese patients diagnosed with OSA with an indication of bariatric surgery and to assess an association between them.

Method: All morbidly obese patients in whom bariatric surgery was indicated between 1/05/2002 and 1/10/2006 were studied. Morbid obesity was defined by body mass index (BMI) greater than or between 35-39 kg/m² associated with comorbidity. The following variables were prospectively collected and analyzed: age, sex, height, weight, BMI, toxic habits, insomnia and excessive daytime sleepiness, measured by the Epworth Sleepiness Scale. All patients underwent nocturnal respiratory polygraphy for the assessment of OSA.

Results: We studied 145 patients (70% women) with a mean age of 42 years (range 19-69) and a mean BMI of 46±5.9. The prevalence of OSA was 95%. The prevalence of somnolence and insomnia in patients who suffer from OSA was 39% and 28% respectively. There was no statistically significant relationship between insomnia and somnolence (p = 0.378). The association between OSA, somnolence and insomnia are shown in Table 1.

Relationship between OSA, somnolence and insomnia

<table>
<thead>
<tr>
<th>AH1 5-14</th>
<th>AH1 15-29</th>
<th>AH1 ≥30</th>
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</thead>
<tbody>
<tr>
<td>Somnolence (yes)</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Insomnia (yes)</td>
<td>20</td>
<td>27</td>
</tr>
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</table>

Conclusions: The prevalence of daytime sleepiness and insomnia in patients with morbid obesity with bariatric surgery indication and OSA is high but we have not found a statistically significant relationship between both clinical entities.
Results: 52 patients, 41 (79%) women, 11 men (21%), mean age 44-24±9.78 years. 48 (92%) with preBS AHI >10, 4 cases (8%) with SaO2 disorders.

9/52 cases (49%) improved or solved their OSA. In 3 cases the AHI postBS was >10, but improved from severe to mild. 4 cases with SaO2 disorders and AHI >10 correct postBS. No patient with IAH postBS.<br>

Conclusions: 1. BS solved completely the OSA in most of the patients (40/52, 77%) and improved it in all of them. 2. No statistical difference was observed in weight loss before and after BS and in all BS and preBS >10 had a high preBS AHI (mean 66.6), significantly higher than patients with AHI <10 postBS. Were not difference according to BMI-preBS and weight loss.

P2258
Objective assessment of sleep pattern and daytime sleepiness during Ramadan fasting in Muslims and non-Muslims
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Background: Studies using sleep diaries have shown a delay in bedtime and rise time during Ramadan. However, no objective study has assessed sleep pattern during Ramadan in a free living environment.

Objectives: To assess the effect of Ramadan and its attendant lifestyle changes on: circadian changes in sleep, and energy expenditure in Muslims and non-Muslims.

Methods: The ArmBand was used to assess the circadian changes in sleep and energy expenditure for 3 weeks, during a baseline period (BL, one week before Ramadan), the first week (R1), and the second week (R2), of Ramadan, in eight Muslims and eight non-Muslim volunteers. The ArmBand is a validated metabolic body monitoring system that records sleep and total energy expenditure. A 29-items questionnaire concerning sleep was collected as well. In addition, Opatiart was used to objectively assess daytime drowsiness using the John Drowsiness Scale (JDS).

Results: Muslims and non-Muslims were matched for age and body mass index. While the start of work has been delayed for Muslims from 7:30 Am to 10 AM, there was no change in working hours for non-Muslims. When BL, R1 and R2 were compared in Muslims, there was a significant delay in bedtime, and rise time and a significant reduction in total sleep time. No changes were documented in sleep pattern in non-Muslims. No changes in daytime sleepiness were documented in both groups using the Epworth sleepiness scale and the JDS.

Conclusion: Changes in sleep pattern in Muslims could be related to changes in lifestyle like the changes in working hours. There is no objective evidence of increased sleepiness during fasting.

P2259
Decreased ventilatory response to carbon dioxide by steady state in patients with myotonic dystrophy type I compared to healthy subjects
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Background and objective: Ventilation is exclusively sensitive to increased PCO2. Carbon dioxide produces its effects by stimulating both central and peripheral chemoreceptors. The testing of such ventilatory response to CO2 can be achieved either by steady state or rebreathing (Read) methods. In order to test the hypothesis based upon abnormality of the central ventilatory control mechanisms in myotonic dystrophy, contributing to chronic alveolar hyperventilation, we compared the ventilatory response to CO2 between control subjects and patients with myotonic dystrophy type I (MD1).

Methods: Ventilatory response to CO2 was achieved in a steady state while breathing gas mixtures containing 3% and 6% of CO2. Each concentration was successively inhaled during 5 minutes following spontaneous breathing room air.

MONDAY, SEPTEMBER 26TH 2011
for at least 10 min. While seated in a comfortable chair, ventilation and PETCO2 were continuously recorded.

Results: Twenty one controls and 51 MDI patients were studied. In controls mean ventilatory responses to CO2 were 1.81 L/min/mmHg ± 0.71 (CO2=3%) and 1.25 L/min/mmHg ± 0.72 (CO2=6%). In MDI patients mean ventilatory responses to CO2 were 0.71 L/min/mmHg ± 0.46 (CO2=3%) and 0.75 L/min/mmHg ± 0.43 (CO2=6%). For both concentrations, ventilatory response to CO2 was significantly lower (p<0.01) in MDI patients than in controls.

Conclusion: This control study confirms the decreased ventilatory response to CO2 in MDI patients using the alternative steady state method. Further studies are needed to define more precisely the role of the impairment of the central ventilatory control in the course of the disease.

P2260
The relationship between testosterone, obesity and depressive mood in obstructive sleep apnea (OSA) postmenopausal women
Raluca Mihaela Bercea1,2, Elena Cojocaru2, Traian Mihaescu1,2, Tatiana Lamon, Sandrine Pontier, Laurent Tetu, Daniel Riviere, Alain Didier.

Background: The relationship between respiratory sleep disorders and menopausal state in women is not well supported; only that obese female have higher androgen levels then non-obese females.

Aim: The aim of our study was to illustrate the link between OSA severity, serum total testosterone level and depressive mood in obese postmenopausal women.

Material and method: The present study included 13 severe OSA female patients (apnea hypopnea index (AHI) >30 events/h) with obesity (body mass index (BMI) >30 kg/m²), ages between 53 and 60 years, for least two years of amenorrhea. All patients fulfilled Beck Depression Inventory (BDI). Serum total testosterone level (T) was performed from blood samples collected in the morning after wake up. Control group selected consisted in 10 non-OSA females with same characteristic with study group.

Results: We found significant correlations between T level and BMI (r=0.363, p=0.019), without correlation between T level and AHI or BDI (p>0.05). It was remarked a strong positive correlation between BDI score and BMI (r=0.720, p=0.006). Test scores no differences between two groups in testosterone level (OSA group 0.757±0.28 ng/dl vs. non-OSA group 0.625±0.19 ng/dl, p=0.226), but significant differences for BDI score (OSA 9.69±5.15 vs. non-OSA 4.3±2.16, p=0.005).

Conclusion: Our study reveals no effect relationship between OSA severity and serum testosterone level. Testosterone level is positive correlated with obesity. Depressive mood is induced by OSA severity, without relation with testosterone level. Our results are needed to elucidate androgens involvement in severe OSA postmenopausal women.

P2261
Mean platelet volume in patients with obstructive sleep apnea syndrome and its relationship with cardiovascular diseases
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Obstructive Sleep Apnea Syndrome (OSAS) is an independent risk factor for the development of cardiovascular event and hypertension. Mean Platelet Volume (MPV), an indicator of platelet activation and aggregation which are closely related with cardiovascular diseases (CVD). We aimed to show the relationship between OSAS and MPV with CVD. The medical records of 205 subjects who were admitted for the sleep study were evaluated. OSAS was diagnosed by polysomnography if Apnea-Hypopnea Index (AHI)>5. MPV calculated from blood samples. According to AHI, individuals in whom AHI=5 were recruited as group 1 (control group), those in whom AHI=5-15 group 2 (mild OSAS group), those in whom AHI=15-30 group 3 (moderate OSAS group), those in whom AHI>30 group 4 (severe OSAS group). Of the subjects 137 (67%) were male, 68 (33%) were female and the mean age was 53.0±14.1years. Those were 35 (17%), 20 (10.2%), 40 (20.4%) and 108 (52.6%) in group 1, 2, 3 and 4 respectively. There were significant differences in terms of coronary artery disease and hypertension between all patients (p<0.05) Except group 1 and 2, other groups showed a significant increase in MPV was detected while the severity of OSAS increased (group 1=9.3±0.7, group 2=9.4±0.8, group 3=9.5±1.1, group 4=10.2±1.2; p for trend 0.03). We have shown that MPV significantly increase in patients with OSAS which is an independent risk factor CVD. MPV may use as a marker to predict CVD in OSAS.

P2262
Congenital central hypoventilation syndrome (CCHS): A case of late onset presentation
Tatiana Lamon, Sandrine Pontier, Laurent Tetu, Alain Didier.

Congenital central hypoventilation syndrome (CCHS) or Ondine’s curse is a rare autosomal dominant disease, characterized by disorders of the autonomic nervous system, with abnormal ventilatory responses to hypercapnia and hypoxemia. PHOX2B has been identified as the major disease causing gene for CCHS. It results from polyalanine repeat expansion mutations. It typically occurs in the newborn period, but some cases have been described on adults (late onset CCHS) and reflects the variable penetrance of PHOX2B mutations.

A 48 year-old woman presented after an ovarian cyst surgery a severe hypventilation requiring intubation. Arterial blood gas revealed a PO2 of 50 mmHg, a PCO2 of 80 mmHg and a pH of 7.22. Past medical history indicated poor apparent symptoms for few years. These included apneas, fullly sleep and awakening with headaches. Physical examination and pulmonary function tests, lung tomography, magnetic resonance imaging of the brainstem were normal. Polysomnography revealed many central and obstructive apneas and hypopneas (apnea-hypopnea index of 22/h) with severe hypoxemia (SpO2 average 75%) and hypercapnia (transcutable CO2 85mmHg). Non invasive ventilation was initially poorly tolerated. Finally, she responded to an adaptive servo ventilation. Hypoxia and hypcapnia tests showed no adaptation of the ventilatory response. Genetic analysis showed a heterozygous five alanine expansion mutation of the 20-residue polyalanine tract in exon 3 of the PHOX2B gene.

The diagnosis of late onset CCHS should be considered in patients with unexplained hypventilation after anesthia, and physiologic evaluations documenting abnormal ventilatory response should be completed. The presence of a PHOX2B mutation confirms the diagnosis.

260. Obstructive sleep apnoea: clinical aspects I

P2263
Investigating for dyslipidemia in those being referred for suspected obstructive sleep apnoea
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Introduction: Abnormal lipid metabolism is a major risk factor in the development of coronary artery disease. Dyslipidemia is present in many subjects with Obstructive Sleep Apnoea Syndrome (OSAS) and an independent association between the two has been observed in a number of studies. Patients referred for inpatient polysomnography in our unit are screened by a fasting lipid profile. This study aims to evaluate the rates of dyslipidemia in this population and to compare OSAS and non-OSAS populations.

Methods: A retrospective review of 285 consecutive subjects (78.6% male, 21.4% female) referred for sleep assessment was performed. Laboratory results, polysomnograms and charts were analysed.

Results: 89 out of the 285 subjects (31.2%) were on a statin and were excluded from further analysis. Of the 196 not on a statin, all had a fasting lipid profile performed. 156 (78.6%) had a positive sleep study, while 40 (20.4%) were negative for OSAS.

OSAS No OSAS p-value
Age 49.2 49.1 0.960
BMI 37.9 30.8 <0.001
AHI 40.55 33.33 <0.001
Total Cholesterol 5.15 5.18 0.890
Triglycerides 1.86 1.57 0.090
LDL cholesterol 3.25 2.99 0.064
HDL cholesterol 1.03 1.39 <0.001

Conclusion: OSAS patients have lower HDL cholesterol levels, but no significant difference in total cholesterol, triglycerides or LDL levels. We recommend to continue measuring fasting lipid profiles in this population. A possible confounding factor in our study is BMI.

P2264
Correlation between excessive daytime sleepiness and the risk for obstructive sleep apnea with academic performance among medical students at UP-PGH Mary Jane Sandagon, Ma. Philina Pablo, Manuel Jorge. Internal Medicine, Pulmonary Section, University of the Philippines- Philippine General Hospital, Manila, Philippines

Objective: This study aims to determine if there is any relationship between daytime sleepiness and risks for obstructive sleep apnea (OSA) with students’ academic performance.

Methods: A self-administered validated questionnaire (consisting of Profile, Sleeping habits, Berlin Questionnaire, and the Epworth Sleepiness Scale) was distributed to duly enrolled medical students from Level 1 to 6 of the University of the Philippines College of Medicine SY 2009-2010. The general weighted average of each student at the end of the 2nd semester school year 2010 was obtained and correlations were determined.
**Results:** There were 458 (64.4%) patients who participated in the study out of the 711 daily enrolled medical students for academic year 2009-2010. Of the participants, 77.3% had abnormal daytime sleepiness ranging from mild to excessive. There was poor correlation between levels of daytime sleepiness and academic performance (Pearson’s correlation coefficient 2.5). There was also poor correlation between risk for obstructive sleep apnea and academic performance gauged by using grade point average (Pearson correlation coefficient 0.86).

**Conclusion:** The present study shows that there is no significant statistical correlation between excessive daytime sleepiness or risk of obstructive sleep apnea and academic performance of medical students as measured by their general weighted average.

**P2265**

**Mortality in young and old subjects with obstructive sleep apnoea with and without comorbidities**

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Increasing obstructive sleep apnoea (OSA) severity has been reported to be associated with a progressive increase in mortality excess, particularly among young subjects. It is unclear if in older subjects apnoeas are less harmful than in younger subjects, or if comorbidities overcome and obscure the effects of OSA on mortality. Medical records of 1023 subjects studied for suspected OSA between 1991 and 2000 were retrospectively evaluated. During the first months in 2009 their state of survival or possible date of death was enquired. Information about 810 subjects (age: 53.2 ± 11.6 years, 629 M) was obtained. In the whole sample, survival was associated to comorbidities and age, but not to AHI or lowest nocturnal SaO2. Among subjects aged <50 (n=315), 87% did not have comorbidities other than hypertension; in subjects ≥50 (n=89) this percentage decreased to 56% (p<0.001).

In the subgroup of the younger subjects without comorbidities (n=273), a lowest nocturnal SaO2 value <90% was associated to worse survival (96.1% vs 10 and 87.6% vs 15 years) as compared to values between 70 and 84% (survival respectively 100% and 85% vs 15 years) (p<0.05).

A similar association was not found among older individuals nor among subjects with comorbidities. These data suggest that among subjects ≤50 increasing OSA severity does not worsen mortality even in subjects without comorbidities.

**P2266**

**Relationship between the reduced ventilatory response to CO2 and the impairment of the lung function in myotonic dystrophy patients**

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Introduction: Myotonic dystrophy type 1 (MD1) is a genetic disorder that shares many cardiovascular risk factors with metabolic syndrome. This study aimed to evaluate the possible association of OSA severity with metabolic syndrome, Insulin resistance and Hs-CRP.

Methods: We evaluated 90 subjects who suspected for OSA (54.92 ± 10.3 years). Blood sampling was taken after 12 hours fasting for glucose, insulin, high-density lipoprotein- (HDL) cholesterol, triglycerides, low-sensitivity C-reactive protein (Hs-CRP), and then Overnight polysomnography was done. Insulin resistance was assessed by the homeostatic model (HOMA) and metabolic syndrome was evaluated according to The National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III), and subjects categorized by OSA severity. We compared three groups: (a) without OSA, mild OSA and moderate to severe OSA.

Results: 28 subjects hadn’t OSA, 28 and 34 subjects had mild and moderate to severe OSA, respectively. Metabolic score was 3.29 ± 1.1, 3.07 ± 1.27 and 3.59 ± 0.48 in subjects without OSA and mild OSA and moderate to severe OSA, respectively (p=0.13 ± 0.22). HOMA index was 56.87 ± 5.84, 106.42 ± 199 68 and 96.23 ± 127.81 (p =0.33 ± 0.37) and hcr-SP index was 1.62 ± 1.8, 2.10 ± 2.24 and 2.36 ± 2.38 (mg/dl=0.21 ± 0.38) order in above three subjects. There was significant association between metabolic score and HOMA index (p=0.01) and also between metabolic score and hcr-SP level (p=0.02).

Conclusion: Although Hs-CRP, insulin resistance and metabolic syndrome increased with OSA severity but there was no significant association between apnea hypopnea index and Hs-CRP, insulin resistance and metabolic syndrome.

**P2268**

** Oxygen desaturation is associated with diabetes mellitus in patients with obstructive sleep apnoea**

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**Objective:** Obstructive sleep apnea (OSA) is associated with impaired glycemic control. The aim of the study was to evaluate the contribution of oxygen desaturation in the association of diabetes mellitus (DM) OSA.

**Methods:** The study was conducted between January 2008 and May 2010 in sultan Qaboos University Hospital, department of clinical physiology.

The data were collected using electronic medical records and sleep study report. Hypoxia desaturation (SaO2 <90%) was calculated by the number of desaturation dips from wakefulness level in addition to SaO2 <90%.

**Results:** The total number of cases was 180 (116 males & 64 females) with mean age 43±17 years. Female patients were more obese than males (BMI=32.2±2.36 kg/m2, 32.7±2.8 kg/m2 respectively, p<0.005). The mean apnea/hypopnea index (AHI) was 31±31 and mean Epworth sleepiness scale (ESS) was 11±5. There was significant association between diabetes mellitus (DM) and AHI (median for diabetic 39 Vs 18 for non-diabetic, p<0.001). There was no significant association between diabetes and oxygen desaturation index (median for diabetic 25 Vs 9.6 for non diabetic p=0.02) and it becomes more significant with severe desaturation (SaO2 <90%) (median for diabetic was 50 Vs 4 for non diabetic p=0.002). There was weak association between body mass index and DM (p=0.05) in this population sample. Nevertheless, there was no association between daytime sleepiness (ESS) and the diabetes (p=0.05).

**Conclusion:** The study showed that Obstructive sleep apnea is associated with diabetes mellitus. OSA patients with more severe Oxygen desaturation are at greater risk of developing diabetes.

**P2269**

**Systemic inflammation and vascular dysfunction in patients with OSA**

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**Introduction:** Our hypothesis is that systemic inflammation and endothelial vascular dysfunction in OSA patients are associated. Therefore our primary objective was to be able to establish the etiological association between them.

**Materials and methods:** Observational case control study in OSA patients and healthy individuals. All of them were tested for serum and urinary markers. Peripheral arterial tonometry by oscillometric sphygmomanometer (ENDO-PAT 2000) was used to measure endothelial dysfunction and arterial stiffness values (Reactive Hyperemia Index-RHI and Augmentation Index-AI).

**Results:** This study involved 42 participants (30 with OSA and 12 healthy controls). Mean age: OSA 61.7, controls 50.4 (p=0.02). Mean BMI: OSA 31.8, controls 26.1 (p=0.01). The OSA severity rate was severe in 54%, low-moderate in 11%, mild in 9% and low in 11.9% of the sample. The results for the serum and urinary markers (Mann-Whitney test) comparison with median and quartiles were the following: CRP (OSA 0.5 controls 0.3, p=0.15), leucocytes (OSA 7500, controls 6000, p=0.18), D-dimer (OSA 339, controls 252, p=0.18), fibrinogen (OSA 401, controls 318, p=0.0007) and microalbuminuria (OSA 7.6, controls 4.7, p=0.12).

No statistically significant differences in arterial stiffness (IA, OSA 19, controls 13.5 p=0.3) neither in vascular endothelial dysfunction (RII, OSA 1.50 control 1.72 p=0.2) were found, although its value was lower than what is considered significant for endothelial dysfunction (<1.67).

**Conclusions:** An association between OSA and cardiovascular risk can be established by measuring the inflammatory marker fibrinogen, and by taking into consideration the data that suggest that endothelial dysfunction may be present.

**Disclosure:** The authors report no conflict of interest.
The changes of serum adipocytokines levels in patients with OSAHS
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Background: Obstructive sleep apnea hypopnea is associated with obesity. Adipocytokines which were secretion by fatty tissue can influence energy metabolism all over the body and the development of obesity. Apelin, NPY and A-FABP were adipocytokines discovered for these last few years. They may participate in the generation and development of OSHAS, especially obesity combined OSHAS.

Objective: To investigate the relationship between adipocytokines (Apelin, NPY and A-FABP) and obstructive sleep apnea-hypopnea syndrome (OSHAS).

Methods: Patients underwent polysomnography were recruited and divided into OSHAS group and non-OSHAS group. Each group was divided into obesity, hyperventilation and normal body weight arms according BMI. OSHAS group was divided into mild, moderate and severe arms. Plasma Apelin, NPY, A-FABP (ng/ml) levels of all arms were tested and compared.

Results: Plasma adipocytokines levels of OSHAS group were positively correlated with BMI, while negatively correlated with Lsao2 and Msao2 in OSHAS group.

Conclusions: Obesity can cause the increase of plasma Apelin, NPY and A-FABP levels. These three adipocytokines levels were positively correlated with the severity degree of OSHAS.

Deregulation of carbohydrate metabolism in patients with sleep apnea
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Material and methods: The study included 103 new patients with the following characteristics of age: BMI 30.2±5.8 kg/m², neck circumference 42.6±7 cm, Epworth 11±10, AH1 33±27/h, DI 34±28/h, mean SpO2 91±6%, minimum SpO2 76±14%, CT 90±22%. Diabetic patients were excluded.

Results: Patients underwent blood tests and sleep studies.

Conclusions: When comparing a group of patients with OSA to a control group, there were significant differences in NGSP HaA1c and IFCC HaA1c (p<0.037). There was significant linear correlation between glucose and age (r=0.21). NGSP HaA1c and IFCC HaA1c (r=0.07), minimum SpO2 (r=0.24), ODI (r=0.37), age (r=0.38). The same for IFCC HaA1c. Insulin with BMI (r=0.39). QUICKI in adipose tissue (r=0.32). BMI (r=-0.47) and with neck circumference (r=0.46). The HOMA-IR index in the OSA group (r=0.46).

To find possible determinants of NGSP HaA1c (%) the following multiple linear regression model with AHI (r=-0.28), with ODI (r=-0.30), with BMI (r=-0.47) and with neck circumference (r=0.38). The same for IFCC HaA1c. Insulin with BMI (r=0.39).

Results:

Conclusions:

The changes of serum adipocytokines levels in patients with OSAHS

Effect of unilateral lingual paralysis on swallowing and breathing coordination
Yacine Ouahchi, Jean Paul Marie, Eric Verin. Laboratoire de Chirurgie Experimenterale, Faculté de Medecine et de Pharmacie de Rouen, Rouen, France

Introduction: The tongue play an important role in swallowing, phonation and respiration. A motor lingual deficit is seen in many neurological disorders. However, its implication on swallowing and breathing coordination remain unknown.

Aim: The aim of this work was to study the ventilatory pattern during swallowing in rats with unilateral tongue paralysis.

Methods: The study was carried out on 10 wistar rats. Respiratory variables in unrestrained and healthy rats were measured during water swallowing using whole-body plethysmography. This procedure was repeated for all rats before and after the unilateral section of the hypoglossal nerve (HI). Parameters studied were swallowing frequency and occurrence during inspiration or expiration, tidal volume (VT), total time of ventilatory cycle (TT) and respiratory drive (VT/TT).

Results: A difficulty of leaking was observed in all rats after unilateral hypoglossal nerve section. The main finding was a decrease of respiratory rhythm and ventilatory drive during swallowing after hypoglossal nerve section. Swallowing rate (17±5/15sec) and occurrence in phases of respiratory cycles did not change. Conclusion: This study demonstrates that swallowing difficulties and aspiration decrease ventilatory drive during swallowing that can be considered as a mechanism neurologically determined to protect the pulmonary function.

The relationship between obstructive sleep apnea hypopnea syndrome and insulin resistance, vascular complications in patients with type 2 diabetes mellitus
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Background: The episodes of hypoxia/reoxygenation caused by OSAHS is associated with a series of metabolic changes, and might be involved in the pathogenesis of type 2 diabetes mellitus (T2DM).

Methods: The subjects were poorly controlled type 2 diabetes mellitus from August 2009 to January 2010 in the Endocrine ward of Beijing Chaoyang Hospital. We recorded the clinical information of all subjects. Fasting venous blood samples was obtained after an overnight fast. Polysomnography (PSG) monitoring,oral glucose tolerance test (OGTT), vascular ultrasound were performed in all the subjects.

Results: 96 type 2 diabetic patients were recruited in our study, 78 subjects (81.25%) were diagnosed as having OSAHS after PSG study. The insulin resistance index (HOMA-IR), which was significantly higher in the moderate and severe group versus the control group. Multiple stepwise regression analysis showed that AH1 and AUCcp was positively correlated (R=0.323, p=0.001), both AH1 and BMI were positively correlated to HOMA-IR (R=0.007 and 0.23, respectively). The percentage of patients who had atherosclerosis were significantly higher in patients with severe and moderate OSAHS than non-apnoic patients.

Conclusion: OSAHS is positively related to insulin resistance, and closely related to the incidence of macrovascular complications in the patients with type 2 diabetes mellitus.

Oxidative stress in obese children with sleep-disordered breathing
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Background: Sleep-disordered breathing (SDB) is prevalent in obese children. It is an independent risk factor for the metabolic syndrome. Oxidative stress is a possible linking mechanism and is reflected by serum uric acid (UA).

Aim: In this prospective follow-up study we focused on the effects of SDB on oxidative stress in childhood obesity, before and after weight loss treatment.

Methods: Obese children, attending an in-patient weight reduction program, between 10 and 18 years were included consecutively. All subjects had baseline and 1 follow-up visit after 4-6 months of weight loss. UA was measured at both visits. A polymyography was performed at baseline and repeated in case of oxygen desaturation index (ODI) ≥ 2 at admission.

Results: 132 obese patients participated. Median age was 15.4 years (10.1-18.0). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.025) and BMI. At baseline, UA concentration correlated negatively with total sleep time (r=-0.24, P=0.049). At baseline, UA concentration correlated negatively with total sleep time (r=-0.32, P=0.002). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001). At baseline, UA concentration correlated negatively with total sleep time (r=-0.24, P=0.049). UA concentration correlated negatively with total sleep time (r=-0.32, P=0.002). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001). At baseline, UA concentration correlated negatively with total sleep time (r=-0.32, P=0.002). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001). At baseline, UA concentration correlated negatively with total sleep time (r=-0.26, P=0.001).
Conclusion: There exists a significant association between UA and ODI at base-
line, even after controlling for BMI z-score. Changes in ODI after treatment are
reflected by changes in UA, independent of the degree of weight loss.

P2276
Cognitive learning function in OSA children
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Introduction: Obstructive Sleep Apnea (OSA) in children is associated with
learning problems, as attention and memory.
Aim: To assess learning, memory and attention function in OSA children.
Methods: OSA children (IAH>4 or LA>1), both genders, aged 6 to 12 years, were
submitted to psychological learning test (symbol, digits and code – WISC III
Wechsler Intelligence Scale for Children). Test result were pondered for age,
10 points were considered normal, <8 as suspicious, <= 7 as disturbed learning
needling specialized support. WISC results were correlated to age, gender, IAH
and desaturation index (IDO). Children with hearing loss, neurologic disease
or genetic syndrome were excluded.

Results: 30 children, 9 girls, median age 8.5 years, were enrolled. Median IAH
was 11.9 (4 to 65) and mean IDO 12.8 (3.4 to 71). 14 (46%) children, 10 boys,
were considered suspected, 9 (30%) 8 boys, were considered as having learning
disturbance (LD). 67% werde diagnosed LD II or more subareas, showing
global learning dysfunction as discrimination, velocity and attention. There was
no correlation of learning disturbance to IAH or IDO (OSA severity), but it was
correlated to male gender and to older age. 50% of children aged 9 to 12 years
were diagnosed LD.

Conclusion: Learning disturbances are frequent in OSA children, independent
of OSA severity. Exposing time to OSA seems to be an important factor. OSA
children should undergo neurocognitive evaluation.

P2277
Variance over time of the obstructive sleep apnoea syndrome (OSAS) in
patients with acute stroke
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OSAS is a cardiovascular risk factor with a high prevalence in patients with
acute stroke in whom could be related to a worse prognosis and an increased
mortality. The aims are to evaluate the evolution and the prognostic role of OSAS
in stroke patients. This is a prospective study in which a respiratory polygraphic
monitoring was performed on the 3rd month (stable phase). 42 of 52 patients were included (age 69
± 12.5 years, 54.8% male, BMI 27 ± 3.6). Arterial saturation was at SaO2:97% constantly. End Diastole Volume
(EDV), Stroke Volume (SV) and Ejection Fraction (EF%) of left ventricle were measured with an anatomical M-mode echocardiographic method. Data analyzed and compared between quite breathing (time 0) and breathing after two hours of airway obstructions (time 0+2).

Results: The cardiac measurements were compared using the Wilcoxon signed-
rank test. EDV and SV were statistically significant reduced (p<0.05) between
time 0 and time 0+2. EF was reduced but not statistically significant at the same
time period.

Conclusions: In this study our findings suggest that left ventricular function is
affected acutely with reduction of EDV and SV after two hours of airway obstructions
independently of hypoxaemia. These results suggest that in obstructive sleep
apnea, negative intrathoracic pressure which occurs during apnea may contribute
to changes in myocardial mechanics.

P2279
Respiratory symptoms and risk for obstructive sleep apnea in professional
musicians
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Background: Obstructive sleep apnea has detrimental effects on function of left
ventricle. It is also known that large decreases in intrathoracic pressure occur
during obstructive apneas.
The aim of this study was to determine the acute changes in left sided heart function
that occur in response to the decreased intrathoracic pressure in an obstructive
sleep apnea model in rats under condition of normoxia.

Methods: Experiments were conducted in ten male adult Wistar rats weighing
350 gr, which were anaesthetized with Ketamine-Xylazine intraperitoneally. Ani-
mals were breathing after being tracheostomized and connected in a circuit with
an electromagnetic valve which was closing periodically mimicking obstructive apneas.Anterio saturation was at SaO2-97% constantly. End Diastole Volume
(EDV), Stroke Volume (SV) and Ejection Fraction (EF%) of left ventricle were
measured with an anatomical M-mode echocardiographic method. Data analyzed
and compared between quite breathing (time 0) and breathing after two hours of
airway obstructions (time 0+2).

Results: The cardiac measurements were compared using the Wilcoxon signed-
rank test. EDV and SV were statistically significant reduced (p<0.05) between
time 0 and time 0+2. EF was reduced but not statistically significant at the same
time period.

Conclusions: In this study our findings suggest that left ventricular function is
affected acutely with reduction of EDV and SV after two hours of airway obstructions
independently of hypoxaemia. These results suggest that in obstructive sleep
apnea, negative intrathoracic pressure which occurs during apnea may contribute
to changes in myocardial mechanics.

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Athens, Athens, Greece

The results suggest that OSA study in acute stroke can lead to an overestimation
of the prevalence of severe OSA, because it significantly reduces its severity in
the stable phase. This information may be important when taking the decision to
start CPAP treatment in acute stroke. In accordance with previous studies, there wasn’t
found any relationship between OSA presence and the stroke functional outcome
on the 3rd month.

P2280
Obstructive sleep apnea contributes acutely to left ventricular dysfunction
independently of hypoxaemia
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Argiro Antaraki2, Nikos Kostomitsopoulos2, Vaggelis Balafas2,
Argiro Antaraki2, Nikos Kostomitsopoulos2, Vaggelis Balafas2,
Kostas Kostakis2, Spiros Papiris1. 12nd Pulmonary Department, Attikon

Background: Obstructive sleep apnea has been approved for the treatment of Pulmonary
Arterial Hypertension (PAH) in adults, but there are few studies about its effects
in children.

Objectives: To review long-term effects and outcomes of inhaled iloprost treatment
in children with PAH.
P2281
Sildenafil (SIL) reduces serum creatinine (SCr) in patients with pulmonary arterial hypertension (PAH): Relationship to clinical outcomes

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Purpose: Elevated SCr associates with poor outcome in PAH. We retrospectively analyzed the effect of SIL on SCr in PAH patients (pts) from SUPER-1 and -2 studies. SCr was related with 6-walk distance (6MDW), functional class (FC), time to clinical worsening (TTCW), and survival were examined.

Methods: PAH pts received placebo (PBO) or SIL 20, 40, or 80 mg TID in SUPER-1 and open-label SIL titrated to 80 mg TID (as tolerated) in SUPER-2. SCr, 6MDW, FC, and TTCW were assessed at baseline (BL) and wk 12 in SUPER-1; survival was tracked for 3 y in SUPER-2. Analysis of covariance (treatment as a factor; BL value as covariate) assessed SCr change from BL to wk 12 (posthoc). Relationships between SCr ≥ 10% 6MDW increase and ≥1-class FC improvement (using logistic regression) and TTCW and survival (Cox regression) were assessed.

Results: BL characteristics were similar among groups (N=277). PAH was mostly idiopathic (63%) and FC II (39%) or III (58%) patients. SCr increased at wk 12 vs BL with PBO (0.03 mg/dL) and decreased with SIL (-0.001, -0.035, and -0.048 mg/dL for 20, 40, and 80 mg TID, respectively); the difference vs PBO with 80 mg TID was significant (P=0.032). SCr reduction was associated with improved 6MDW (OR 4.74; 95% CI, 1.07–21.05; P=0.04) and FC (OR 6.64; 95% CI, 1.37–32.16; P=0.019). Pts with higher SCr had higher risk of worsening (HR 44.38; 95% CI, 4.74–412.59; P<0.001) and a trend toward higher risk of mortality (HR 2.62; 95% CI, 0.23–30.55; P=0.04).

Conclusion: In posthoc analysis improved with administered SIL 6MDW and FC and reduced risk of clinical worsening.

P2282
Epoprostenol with expanded stability has the same pharmacokinetic and hemodynamic profiles as epoprostenol in healthy subjects

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Pharmacokinetics (PK) and hemodynamics of two formulations of epoprostenol sodium for injection, epoprostenol with expanded stability (EPO-ES, Venelys®) and epoprostenol (EPO, Flolan®), were compared in an open-label, crossover, ascending-dose study in healthy males. Subjects received sequential, 2-hour (h) infusions of EPO-ES or EPO at 2, 4, 6 and 8ng/kg/min. Due to the short half-life (t1/2) of epoprostenol sodium, plasma PK were assessed via the concentration versus time profiles of two primary metabolites, 6-keto-prostacyclin F1α (kPF) and 6,15-diketo-13,14-dihydro-prostacyclin F1α (dDPF). Plasma concentration-versus-time profiles of EPO-ES and EPO with regard to kPF and dDPF were superimposable. KPF and dDPF had similar elimination half-lives (t1/2a). Both formulations were comparable. Geometric means of the total area under the curve (AUC() for KPF, were 2011 and 1972pg/h/mL (90% CI of geometric mean ratio (GMR) 97, 107, 128, 1972pg/h/mL, (90% CI of GMR: 94, 111) for dDPF following administration of EPO-ES and EPO, respectively. Similar changes in hemodynamic variables were observed during EPO-ES and EPO infusion. Average maximum increases from baseline were approximately 50% in both cardiac output and cardiac index with either formulation, and 19% and 27% in heart rate for EPO-ES and EPO, respectively. Both formulations had comparable treatment-emergent adverse event (TEAE) profiles. Headache was the most common TEAE reported. Overall, EPO-ES and EPO have the same PK, hemodynamic, safety, and tolerability profiles.

P2283
Switch from sitaxentan to another ERA in ERA patients: Single center short term safety observations

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Background & aims: In December 2010 the Endothelin Receptor Antagonist (ERA) Sitaxentan (SIT) has been withdrawn from the market. Therefore patients with pulmonary arterial hypertension (PAH) had to be switched to other PAH therapies. There are differences in the side effect-profile of the ERAs Ambrisentan (AMB), Bosentan (BOS) and SIT including drug interactions. We describe the short term safety in PAH-patients at our center who were switched from SIT to another ERA.

Methods: All patients switched from SIT to AMB or BOS for more than 4 weeks were included. We collected liver function tests (LFT), INR, WHO functional class (FC) and new side effects.

Results: Patients on SIT (n=16) were seen 13 days (4–32) after the withdrawal notification. Mean duration of SIT therapy was 478 days (93–2332). Patients were switched to AMB (n=10) or BOS (n=6) on the basis of personal experience and expected side effects. Mean follow-up was 41 days.

LFTs under SIT were all within the normal range and remained normal in all but one patient who had ALAT increase from 13 to 242 U/L on BOS, normalizing after BOS cessation. The WHO FC did not change in any patient. Three patients complained about new or worsening peripheral edema, 2 on AMB and 1 on BOS. In 4 out of 12 patients receiving oral anticoagulation who were in therapeutic range under SIT, the INR dropped below 2 after switch to AMB (1) or BOS (3). One patient died suddenly 10 days after switch to BOS.

Conclusion: PAH-patients who are switched from SIT to another ERA can experience in part serious pathophysiological problems and should be closely monitored.

P2284
Double combination therapy in patients with pulmonary arterial hypertension associated with congenital heart defects

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Purpose: Patients with pulmonary arterial hypertension associated with congenital heart defects (PAH-CHD) are currently treated with targeted therapy. According to recent guidelines PAH-CHD patients with inadequate clinical response should also be treated with combination therapy (CT). We assessed the effects of double CT in a group of PAH-CHD patients.

Methods: In the last 6 years, 43 adult patients with PAH-CHD (age 43±14 ys, 65% females) already treated with monotherapy were included. Twenty-nine were treated with bosentan (125 mg bid) and 14 with sildenafil (20 or 50 mg tid). Twelve patients had a ventricular septal defect, 5 patients had an atrial septal defect, 5 had a patent ductus arteriosus, 8 had combined defects, and 13 had corrected defects. At baseline and after CT (with sildenafil or bosentan according to the first-line treatment) 6-minute walk test (6MWT) and right-heart catheterization were performed.

Results: One patient did not perform 6MWT and another one did not undergo RHC after combination therapy. The table shows the hemodynamic and functional changes after a mean treatment period of 4.8±2.1 months of CT.

<table>
<thead>
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<th>Parameter</th>
<th>B</th>
<th>CFT</th>
<th>p</th>
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<td>mPAP (mmHg)</td>
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<td>86±17</td>
<td>2.54±0.9</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>15±2</td>
<td>85±14</td>
<td>2.84±1.1</td>
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<tr>
<td>mPAP (mmHg)</td>
<td>0.002</td>
<td>0.06</td>
<td>0.013</td>
</tr>
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mPAP: mean pulmonary arterial pressure; mBP: mean blood pressure; Qp: pulmonary cardiac index; PVR: pulmonary vascular resistance; SaO2: systemic arterial oxygen saturation.

Conclusions: CT improves exercise capacity and hemodynamics in patients with PAH-CHD already on monotherapy. Sequential CT appears to be an appropriate approach also in patients with PAH-CHD.

P2285
ACE2 activation improves pulmonary endothelial function and attenuates monocrotaline-induced pulmonary hypertension

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Angiotensin converting enzyme 2 (ACE2), a member of the vasoprotective axis of the renin angiotensin system, protects the lungs against acute lung injury and pulmonary hypertension. The present study was undertaken to test the hypothesis that activation of endogenous ACE2 by diminazene aceturate (DIZE), a putative ACE2 activator would prevent and reverse monocrotaline (MCT)-induced pulmonary hypertension. In the prevention protocol, DIZE was administered at the same time as MCT, while for the reversal protocol DIZE was injected after 3 weeks of MCT
administration. A single subcutaneous injection of MCT (50mg/kg) resulted in elevated right ventricular systolic pressure (RVSP) associated with the development of right ventricular hypertrophy (RVH). DZIG administration (15mg/kg per day) significantly prevented increases in RVSP (Control: 31±3 mmHg; MCT: 57±7 mmHg; MCT+DIZE: 41±4 mmHg; n=5-8; p<0.05) and attenuated RVH (Control: 0.23±0.04 mmHg; MCT: 0.43±0.03 mmHg; MCT+DIZE: 0.26±0.01 mmHg; n=5-8; p<0.05). In subgroup analysis, we observed a 63% decrease in acetylcholine-induced vasorelaxation of the pulmonary arteries from MCT-challenged rats. DIZE treatment resulted in 50% improvement in acetylcholine-induced vasorelaxation, signifying better pulmonary endothelial function. Furthermore, DIZE treatment reversed MCT-induced increases in RVSP (Control: 33±2 mmHg; MCT: 78±6 mmHg; MCT+DIZE: 50±5 mmHg; n=7-11; p<0.05) and RVH (Control: 0.24±0.02 mmHg; MCT: 0.54±0.02 mmHg; MCT+DIZE: 0.44±0.03 mmHg; n=7-11; p<0.05). These data suggest that DIZE’s primary protective effects are mediated by ACE activation, other though off-target effects may also contribute.

P2286

Effect of treatment on exercise endurance tolerance and ventilatory efficiency in patients with pulmonary arterial hypertension (PAH)

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Incremental Cardiopulmonary Exercise Test (CPET) or 6-Minute Walking Test (6’MWT) are utilized for the evaluation of Pulmonary Arterial Hypertension (PAH) patients, although the parameters obtained (e.g. peak oxygen uptake - V’O2Peak - and walking distance, respectively) have a different predictive value, depending on outcomes of interest (e.g. prognosis, response to therapy). We evaluated the effect of treatment on principal indexes obtained during CPET, constant work rate test on cycle ergometer (CWR) (e.g. endurance time, Tlim), and 6’MWT. Methods: Nine naive PAH pts (age 41±15.0 years; mean PAP 51±15 SD mmHg) underwent, before (PRE) and after (POST) treatment, CPET, CWR (80% max load at PRE-CPET) and 6’MWT. V’O2, CO2 output (V’CO2), ventilation (V’E), heart rate (HR) and other derived parameters (V’E/V’CO2) were measured breath-by-breath (Quark b2, COSMED, Rome, Italy); PRE- and POST-values at peak and at isotime were compared (paired t-test). Results: During CWR, POST-Tlim resulted significantly longer than PRE-Tlim (POST-Tlim 11’24”±6’07” vs PRE-Tlim 5’38”±3’03”; p<0.01) and POST-V’E/V’CO2 at peak and at isotime was significantly lower compared to PRE-value at peak (p<0.01 and p=0.02 respectively). During CPET, POST-V’O2Peak was not significantly higher than PRE-V’O2Peak (p=0.06). POST 6’MWT distance resulted significantly higher than PRE-one (p<0.01).

Conclusions: The better POST-treatment exercise tolerance in PAH pts seems to be linked to a ventilatory efficiency improvement, and the parameters obtained at CWR and 6’MWT, compared to CPET, appear to be more sensible to the effect of medical treatment.

P2287

Improved survival in medically-treated chronic thromboembolic pulmonary hypertension

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Background: Although the key for the successful treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary endarterectomy (PEA), the patients who are not indicated for surgical intervention and/or have comorbidities must therefore be medically treated. Recent new medical therapies (new Tx), such as bosantan and sildenafil, may thus be able to improve the outcome of Japanese patients with CTEPH.

Purpose: To clarify the improved survival in CTEPH cases administered new Tx.

Methods: Between 1986 and 2010, 202 patients were diagnosed to have CTEPH at Chiba University Hospital. Ninety-nine patients underwent PEA, while 103 patients were medically treated. 56.5% of the patients diagnosed from 2005-2010 were treated by new Tx., 19.4% of those from 1999-2004, and 8.7% of those from 1986-1998 (p=0.05). We investigated the long-term survival from the diagnos is and prognostic factors in medically-treated CTEPH cases and also examined survival from the initiation of the new Tx.

Results: The patients diagnosed from 2005-2010 showed a significantly improved survival (5-year survival: 87.8%) compared with those from 1999-2004 (72.2%) and from 1986-1998 (56.5%) (p=0.02). The 5-year survival from the initiation of bosantan (n=15) and sildenafil (n=24) was 90.0%, 84.2%, respectively. A multivariate analysis revealed a lower pulmonary vascular resistance (p<0.0001), no comorbidities (p=0.0009), a peripheral type (p=0.02), and recent patients (p=0.02) to be significantly better prognostic factors.

Conclusions: The survival in medically treated CTEPH cases was found to have improved due to the administration of new medical therapies.
to associate a specific PAH treatment with a highly active anti-retroviral therapy (HAART).

Recent studies report some excellent response to Bosentan treatment, with hemodynamic normalisation and long term benefit of this treatment. But, there is no data upon specific treatment discontinuation.

We report here two patients with persistent remission after Bosentan cessation. Patients were women, IV drugs users, one of African origin 36-years old, the other Caucasian of 46-years old. Diagnosis of PH was performed respectively one year and twenty years after diagnosis of HIV infection. Both patients received HAART and Bosentan.

Because of persistent normalization of hemodynamic and functional parameters, bosentan was withdrawn respectively 5 and 1 years after beginning. Both patients remain asymptomatic with normal hemodynamic results respectively at 42 and 12 months after bosentan discontinuation.

Data are illustrated on figure for both patients.

Conclusion: We propose herein to go one step further in PAH treatment with these two cases of cured PAH-HIV, despite more than three years of Bosentan discontinuation. But we recommended not stopping treatment without complete clinical, hemodynamic and immunological persistent normalisation during at least one year.

P2390

Effects of BAY 41-8543 and sildenafil on right heart structure and function in pulmonary artery banding mice

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Background: Right ventricular (RV) pressure over-load causes RV remodeling. Impaired NO/GMP signaling is involved in the pathogenesis of LHV hypertrophy. We assessed the effects of the soluble guanylate cyclase (sGC) stimulator BAY 41-8543, the PDE5 inhibitor sildenafil, and combination treatment on RV function and RVHI in an animal model of chronic pressure-overload.

Methods: RVHI was induced by pulmonary artery banding (PAB) in mice. Treatment started 7 days after surgery for 14 days, after which RV morphology and function were studied using Magnetic Resonance Imaging. Fibrosis was assessed by histology.

Results: BAY led to RV dysfunction (decreased RV stroke volume (40.5 vs. 23.0 ml [Sham vs. PAB]) and decreased RV ejection fraction (70.0 vs. 43.0%). Treatment with sildenafil did not change RV function, whereas BAY 41-8543 and combination treatment led to significant improvements (RV stroke volume: 23.0 vs. 12.1 vs. 31.1; RV ejection fraction: 43.3 vs. 54.1 vs. 55.7 vs. 63.8 [all values as%; placebo vs. sildenafil vs. BAY 41-8543 vs. combination treatment]). PAB mice showed an increased RV/(LV-S) ratio (0.25 vs. 0.39). Drug treatment had no effects on collagen content, whereas BAY 41-8543 and combination treatment significantly improved RV mass, BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass, whereas BAY 41-8543 and combination treatment significantly improved RV mass.

Conclusions: Even though none of the treatments led to significant changes in RV mass, BAY 41-8543 and combination treatment significantly improved RV function, accompanied by decreased fibrosis.

P2293

Optimization of tissue targeting properties of macitentan, a new dual endothelin receptor antagonist, improves its efficacy in a rat model of pulmonary fibrosis associated with pulmonary arterial hypertension

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Introduction: We investigated the efficacy of macitentan, a new tissue-targeting dual endothelin (ET) receptor antagonist, in a model of pulmonary fibrosis associated with pulmonary hypertension and compared it with dual ET receptor antagonist, bosentan.

Methods and results: Oral administration of macitentan for 19 days dose-dependently decreased lung hydroxyproline content with a statistically significant effect observed at 30 and 100 mg/kg/day vs. non-treated bleomycin rats (n = 8-12). Overall, macitentan (100 mg/kg/day) consistently inhibited the development of pulmonary fibrosis by 18-27% in three independent studies, and decreased right ventricle hypertrophy by 25-28% in two of these three studies. In contrast, bosentan (300 mg/kg/d) inhibited the development of pulmonary fibrosis in only one of the three experiments, by 23%, and had no effect on the development of right ventricle hypertrophy. Administration of radio labelled 14C-macitentan or 14C-bosentan to bleomycin-treated rats showed greater drug distribution in the lung compared to the distribution in healthy animals. Notably, distribution of macitentan into the parenchyma of bleomycin-treated rats was greater than that of bosentan.

Conclusion: Repeated experiments demonstrated that macitentan is more efficacious than bosentan in preventing the development of lung fibrosis and right ventricle hypertrophy. Greater ability of macitentan to distribute into the tissue could explain its improved efficacy profile, as it would achieve a more complete blockade of ET receptors.

P2292

First and second line treatment pattern among pulmonary hypertension patients enrolled in a managed care health plan

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Purpose: To describe first and second line treatment pattern among PH patients enrolled in managed care health plan.

Methods: Data were derived from the MarketScan claims database. PH patients were identified anytime during 4/1/2006 to 3/31/2009 using the ICD-9 claim of 416.X. First line therapy was defined as the first PH-related pharmacy claim within ±12 months of the diagnosis claim. Second line treatment was defined as separate PH-related pharmacy claim post the first line PH-related pharmacy claim. PH-related treatment included prescriptions for high-dose calcium channel blockers (CCBs), endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5is), or prostacyclin analogues (PAs). CCB users had no diagnosis claim of essential hypertension anytime during the study period.

Results: Final study sample was 2,252, with a mean age of 61.2 years (SD±16.41), and 57% females. 46% of PH-patients had CCB as the first line treatment followed by PDE5is (38%), ERAs (13%), and PAs (3%). 16% of the sample had some second line treatment over a 12-month follow-up. Combination therapy was only observed in the CCB-cohort, where 69 patients added an ERA/PDE5i to their current treatment. Switching was most common among ERA (61%) and PA (50%) first line users, with majority switching to PDE5. Total average treatment days for first-line PH- prescription varied from a low of 21 (SD±8.14) days among PA-users to 266 (SD±131.39) among ERA-users, respectively.

Conclusions: CCBs and PDE5s were the most prescribed first line treatment among PH-patients. Future research would need to explore the choice of first line treatment in clinical and economic

410s
P2294
Pulmonary hypertension in patients treated with Src/ABL kinase inhibitor dasatinib
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Methods: The present report summarizes the clinical characteristics and outcomes of dasatinib-associated PH cases from the French PH Registry.

Results: Between 1st January 2008 and 30th September 2010, 11 patients with either a diagnosis of CML and/or a treatment with imatinib, dasatinib or nilotinib were identified corresponding to 2 prevalent imatinib-treated CML patients previously reported by our group and who developed PH prior to treatment with imatinib (Souza et al, Thorax 2006;61:736) and 9 incident patients who were all exposed to dasatinib at the time of PH diagnosis. The lowest estimate of incident PH occurring in patients exposed to dasatinib was 92.9/00 (0.31%), as compared with no incident case reported with imatinib or nilotinib in the same period.

Conclusions: Dasatinib therapy may promote severe pre-capillary PH, suggesting a direct and specific effect of dasatinib.

P2295
Everolimus improves exercise capacity and pulmonary vascular resistance in patients with advanced pulmonary hypertension – A pilot study
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Background: In recent years, pulmonary arterial hypertension (PAH) has been recognized to be a predominantly proliferative process. The inhibitor of the mammalian target of rapamycin (mTOR) everolimus inhibits cellular protein synthesis and growth in cells of the vascular wall.

Methods: Ten patients with PAH (n=8) or chronic thromboembolic pulmonary hypertension (CTEPH) and progressive disease despite therapy with at least two vasodilating drugs were included in a prospective open label pilot study. All patients were treated additionally with everolimus. Safety and tolerability were observed. Pulmonary vascular resistance (PVR) and 6-minute walking distance (6MWD) were considered as primary endpoints.

Results: In two patients study medication was stopped prematurely due to an adverse event. The remaining 8 patients exhibited a significant improvement in PVR (1049±438 vs. 689±235 dynsec/cm²; p=0.004) and 6MWD (246±405 vs. 313±127m; p=0.04) after 6 months of therapy with everolimus.

Conclusion: Antiproliferative with everolimus therapy was tolerated in ten patients in this pilot study. The observed improvements in PVR and in 6MWD may stimulate further consideration of mTOR inhibition in pulmonary hypertension.

P2296
WITHDRAWN

WITHDRAWN

P2297
Ambrisentan improves exercise capacity and symptoms in patients with portopulmonary hypertension
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Introduction: Ambrisentan, a selective endothelin receptor antagonist has been approved in several countries for pulmonary arterial hypertension. No data have been published on the efficacy of ambrisentan on improvement of exercise capacity in patients with portopulmonary hypertension (PoPH).

Methods: We retrospectively analyzed the safety and efficacy of ambrisentan in patients with PoPH in four German university hospitals.

Results: 14 patients with moderate to severe PoPH were included. The median follow-up was 16 months (IQR, 12-21). 6 minute walk tests after 6 and 12 months improved from 376 meters (IQR, 207-440) to 415 meters (IQR, 362-431), respectively. WHO functional class after 1 year of therapy with ambrisentan also improved significantly (p=0.014). No significant changes in blood gas analysis and liver transaminases were detectable.

Conclusions: The present study demonstrates significant improvement of exercise capacity and symptoms without relevant safety concerns during ambrisentan treatment in patients with PoPH.

P2298
Double combination therapy in patients with pulmonary arterial hypertension associated with connective tissue disease
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Background: Pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) is a severe and progressive condition despite the availability of 3 specific classes of drugs: prostanoids (PROST), endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE5-I). Combination therapy (CT) has been proposed for patients with unsatisfactory response to monotherapy.

Aim: To examine the effect of double CT in patients with PAH -CTD who do not achieve an adequate clinical response on monotherapy.

Methods: Between October 1999 and December 2010, 48 PAH-CTD patients in WHO functional class III treated with monotherapy were included. At baseline and after 5±5 months on CT, all patients underwent 6-minute walk test (6MWT) and right heart catherization.

411s
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Results: Mean age was 58±14 years, 85% females. Mean time from initiation of monotherapy to initiation of CT was 18±20 months. Forty (83%) patients received ERA+PDES-I, 5 (10%) received PDES-I+PROST and 3 (7%) received ERA+PROST. Four (8%) patients died before CT assessment. The table shows the haemodynamic and functional changes after CT.

### Table: CT in CTD-PAH patients

<table>
<thead>
<tr>
<th>(n=44pts)</th>
<th>RA (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>mPH (mmHg)</th>
<th>CI (L/min/m²)</th>
<th>PVR (W.U.)</th>
<th>6MWT (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>12.6±5.2</td>
<td>52±11.1</td>
<td>88±11.1</td>
<td>2.2±0.5</td>
<td>12±5.2</td>
<td>312±111</td>
</tr>
<tr>
<td>Double CT</td>
<td>9±4.5</td>
<td>49±11.1</td>
<td>83±11.1</td>
<td>2.6±0.6</td>
<td>10±2.5</td>
<td>317±132</td>
</tr>
</tbody>
</table>

R: right atrial pressure; mPAP: mean pulmonary arterial pressure; mPH: mean blood pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

Conclusions: CT in CTD-PAH patients improves exercise capacity and haemodynamics. However, 8% of patient die after an average of 3.2±1.5 months of CT testifying the persistent severity of the condition.

### P2399

Tadalafil in idiopathic or heritable pulmonary arterial hypertension compared to pulmonary arterial hypertension associated with connective tissue disease

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Patients (pts) with PAH associated with connective tissue disease (APAHT-CTD) have a worse prognosis compared to idiopathic (I) or heritable (HPAH). Our objective was to test the clinical outcomes in these two subgroups. In a 16 week (wk), double-blind, placebo (PBO) controlled trial with blinded 52 wk extension, pts were randomized to PBO, 20 or 40mg tadalafil (Tad) qd (APAHT-CTD: n=54, 21 and 19, respectively; APAHT-I/II: n=54, 50 and 46, respectively; subgroup efficacy analyses included six-month walk test (6MWT, 4Mg) at Wk16 (assessed by rank permutation tests) and clinical worsening (C, PBO and 40mg) at Wk16 and up to 68wks (20 and 40mg). Pts on 20mg without C at 6wks remained on 20mg and all others received 40mg in the extension. Mean changes in 6MWT from baseline to Wk16 were 32m in APAHT-CTD and 58m in APAHT-I/II for 40mg Tad dose. PBO-corrected treatment effects on 6MWT at Wk 16 were 49m in APAHT-CTD (P=0.03) and 22m in APAHT-I/II (P=0.04). The 5% of pts with C in the Tad 40mg and PBO subgroups at Wk16 were 11 and 25% in APAHT-CTD, respectively and 4 and 15% in APAHT-I/II, respectively. In pts who received Tad 20 or 40mg up to 68wks, C was 35% in APAHT-I/II (n=40) and 24% in APAHT-I/II (n=96). Tad 40mg improves 6MWT at Wk16 in APAHT-CTD and APAHT-I/II; however, with PBO 6MWT decreased in APAHT-CTD but not in APAHT pts. In addition, C was numerically less in both Tad groups at Wk16 compared to PBO. At Wk68, C was numerically higher in APAHT-CTD vs. APAHT-I/II. These latter data are consistent with a worse prognosis in APAHT-CTD. Whether more aggressive therapy earlier in APAHT-CTD pts would be efficacious requires further study.

### P2300

Role of exercise cardiac index to predict NYHA functional class, 6-minute walk test distance and survival in idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension

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The aim of the study was to evaluate right ventricular functions in patients by TDI. Methods: Pulmonary haemodynamics and RV functions were evaluated by TDI and Doppler-ECHO in 48 highlanders at altitude of residency (3200-3800 m). All patients were divided into the three groups: 1st group (n=20) - patients with high altitude pulmonary hypertension (PAH) 2nd group (n=20) - patients with HAPH and RV hypertrophy. 3rd group (n=20) healthy highlanders. All subjects underwent clinical examination, ECG, spirometry.

Results: Conclusions: The evaluation of peak systolic and diastolic tricuspid annular velocity using TDI revealed RV hypertrophic diastolic dysfunction in patients with HAPH and RV hypertrophy. The 6MWT is a good predictor of exercise capacity. This variable was also the best survival prognostic factor in our group of patients.

### P2301

Estimation of right ventricular function in highlanders with high altitude pulmonary hypertension and high altitude cor pulmonale

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Tissue Doppler imaging (TDI) is used as additional approach for diagnosis of right ventricular (RV) dysfunction in PH. But RV function obtained by TDI has rarely been investigated in highlanders.

The aim of the study was to evaluate RV functions in highlanders by TDI. Methods: Pulmonary haemodynamics and RV functions were evaluated by TDI and Doppler-ECHO in 48 highlanders at altitude of residency (3200-3800 m). All patients were divided into the three groups: 1st group (n=20) - patients with high altitude pulmonary hypertension (PAH) 2nd group (n=20) - patients with HAPH and RV hypertrophy. 3rd group (n=20) healthy highlanders. All subjects underwent clinical examination, ECG, spirometry.

Results: Conclusions: The evaluation of peak systolic and diastolic tricuspid annular velocity using TDI revealed RV hypertrophic diastolic dysfunction in HAPH patients and RV systolic dysfunction with pseudonormal pulmonary dysfunction in patients with HAPH and RV hypertrophy.

### P2302

Analysis of the cardiac index-PvO2 relationship during vasodilatation challenge as a prognostic factor in pulmonary arterial hypertension

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Background: Mixed venous oxygen pressure (PvO2) is a reflection of the tissue oxygenation state. PvO2 is one of the variables associated to survival in patients with pulmonary arterial hypertension (PAH).

Objectives: Investigate if the relationship CI – PvO2 during vasodilatation challenge (VC) is maintained and whether the type of response has any prognostic implication in PAH patients.

Methods: We analyzed the hemodynamic and gasometrical variables at baseline and during the response to the acute VC at right heart catherization of patients with PAH. According to the results, patients were judged to have an appropriate response (AR) (i.e. higher CI=higher PvO2) or not. The midterm survival in both groups was also analyzed.

Results: We studied 42 patients with PAH (35±5 years; 76% female). For the drug challenge we used adenosine (n=33) and Iloprost (n=9). Patients with AR (n=31) had a significant correlation CI-PvO2 at baseline and during challenge (r=0.67; and 0.52, respectively, p<0.05). In patients with inappropriate response (IR) (n=11) the correlation was significant at baseline (r=0.59; p<0.05) but it was lost during challenge (r=0.72; p<0.05). The correlation delta CI-CI-PvO2 was positive (r=0.41; p<0.05) for those with AR and it was negative for those with IR (r = 0.5; p<0.05). In a preliminary analysis, 5-year mortality appears higher in those with an AR (27.2 versus 15%).

Conclusions: Some patients with PAH have an abnormal tissue oxygenation, which may be uncovered by the analysis of the CI-PvO2 relationship. This finding may be of prognostic significance.
Diaphragm function in experimental pulmonary hypertension

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Introduction: Recently it was suggested that patients with pulmonary hypertension (PH) suffer from diaphragm dysfunction due to increased loading conditions. In the present study we aimed to determine the contractile strength of the diaphragm muscle in PH and control rats. The extensor digitorum longus (EDL) muscle will serve as a control skeletal muscle.

Methods: PH was induced in Wistar rats by a single injection of monocrotaline (60 mg/kg). The diaphragm and EDL (PH n=5; controls n=5) muscle were excised for determination of in vitro contractile properties. Muscle bundles were treated with a relaxing solution (5°C) containing 1% Triton X-100 to permeabilize membranes. Single fibers were mounted on a single fiber apparatus. Maximum force (Fmax), rate constant of force redevelopment (Ktr), as a measure of the cross bridge kinetics, and calcium sensitivity (pCa50) were measured in diaphragm and EDL single muscle fibers.

Results: In the EDL muscle no significant differences were found in Fmax and pCa50. Ktr was significantly higher in PH fibers: 10.86±0.79 vs 15.09±0.74 (p=0.005). The cross sectional area (CSA) of the fibers measured was significantly decreased in PH fibers: 256.1±16.7 vs 196.1±88.82 μm² (p=0.013).

Conclusions: These data suggest a more pronounced effect of PH on the diaphragm muscle compared to EDL. However, more experiments on the diaphragm muscle and fiber type determination is necessary before final conclusions can be drawn.

Diaphragm function in experimental pulmonary hypertension

P2304

A model-based analysis of the effect of hypoxia on regional pulmonary blood flow

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Hypoxic pulmonary vasconstriction (HPV) diverts blood from hypoxic regions of the lung, optimising ventilation/perfusion (V/Q) matching and gas exchange. In the diaphragm, hypoxia is thought to improve HPV via increased oxygen delivery to the tissue and/or HPV becomes less effective in the lung. The aim of the current study was to determine if HPV is present in the diaphragm muscle and if HPV differs from that present in other regions of the lung.

Methods: An animal model of chronic hypoxia was used to study regional pulmonary blood flow distribution. A 7 week period of hypoxia resulted in a 15% reduction in arterial oxygen saturation in the rats. 20 rats were studied (10 controls, 10 hypoxic). Regional pulmonary blood flow was measured using indocyanine green fluorescent microsphere injections. The percentage of the total blood flow to each of the 9 lobes was calculated for each rat.

Results: In the controls, 25% of the blood flow went to the upper lobes, 25% to the lower lobes, and 50% to the right middle lobe. In the hypoxic rats, 20% of the blood flow went to the upper lobes, 30% to the lower lobes, and 50% to the right middle lobe. This was statistically significant (p<0.05).

Conclusions: These results suggest that HPV is present in the diaphragm and is altered by chronic hypoxia in a similar manner to the effect seen in other regions of the lung.

Diaphragm function in experimental pulmonary hypertension

P2305

Association of renal dysfunction with cardiac output and right atrial pressure in pulmonary arterial hypertension

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Background: Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature that results in right ventricular (RV) failure and death. Renal insufficiency is recently identified as a key predictor of mortality in PAH patients [1]. Renal dysfunction is associated with decreased cardiac output (CO) in patients with left heart failure [2], however, little is known about the mechanism of renal dysfunction and its association with venous congestion in PAH patients with RV dysfunction.

Objectives: To investigate the relationship between CO, right atrial pressure (RAP) and estimated glomerular filtration rate (eGFR) in patients with PAH.

Methods: 74 patients underwent baseline right heart catheterization to determine CO and RAP and blood sampling to calculate eGFR. These measurements were repeated in 30 patients after 12±4 months of follow-up.

Results: Mean age was 52±15 years and 73% of subjects were female. Mean eGFR was 88.8±24 ml/min/1.73m², mean CO was 5.1±1.7 L/min and mean RAP was 7.0±4.5 mmHg. Low eGFR at baseline was associated with low CO (R0.46; p<0.001) and high RAP (R=0.20; p=0.042). Multivariate regression analysis showed that CO was an independent determinant of eGFR (p=0.01).

Conclusion: CO is the main determinant of renal dysfunction in patients with pulmonary arterial hypertension and RV dysfunction.

References:

Contrasting cardiopulmonary responses to incremental exercise in patients with schistosomiasis-associated and idiopathic pulmonary arterial hypertension with similar resting hemodynamic impairment

P2307

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Schistosomiasis is the most common cause of pulmonary arterial hypertension (PAH) worldwide. It has been reported that schistosomiasis-associated PAH (Sch-PAH) has better hemodynamic profile at diagnosis and a more benign clinical course as compared with idiopathic PAH (IPAH) [1]. We hypothesized that Sch-PAH patients have better physiological responses to incremental cardiopulmonary exercise test (CPET) than IPAH patients, even at similar resting pulmonary hemodynamic impairment. We performed CPET and hemodynamic study in 8 Sch-PAH and 9 IPAH patients. None of them had received any PAH therapy. There were no significant between-group differences on cardiac index (2.1±0.3 vs 2.4±0.7 L/min, p=0.21), pulmonary vascular resistance (p=0.32) and mean pulmonary artery pressure (p=0.48). However, the peak oxygen uptake (VO2peak) was greater in Sch-PAH (75±21 vs 54±16%pred, p=0.016), as well as the ratio of increases of VO2 to work rate (8.2±1.1 vs 6.8±1.1 mL/min/W, p=0.024). Also, the slope of the ventilatory response as a function of CO2 output was lower in Sch-PAH (41±4 vs 59±18 L²/min², p=0.04), with a shallower heart rate response for a given change in VO2 (88±21 vs 123±39 beats/min², p=0.02), and a greater peak oxygen pulse (p<0.05). In conclusion, Sch-PAH patients had better physiological responses to exercise than IPAH subjects at similar resting hemodynamic profile. Our data suggest a more preserved hemodynamic response to exercise in Sch-PAH, which might explain its better clinical course as compared with IPAH.
P2308

Nitric oxide metabolite flux during exercise in pulmonary arterial hypertension

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Introduction: Exercise-induced pulmonary arterial hypertension (PAH) is a clinically important stage in the spectrum of PAH. The pathophysiology of abnormal pulmonary vascular responses to exercise is poorly characterized. Endogenous nitric oxide (NO) is an important mediator of vasodilation and accumulating data suggests impaired NO signaling in patients with PAH.

Aims: The objective was to test the hypothesis that changes in stable NO metabolites (NOx) in blood during exercise in patients with resting or exercise-induced PAH would differ from NOx in individuals with normal exercise pulmonary arterial pressures. Patients were selected from a population referred to the MGH Cardiopulmonary Exercise Laboratory for invasive incremental cardiopulmonary exercise testing with pulmonary and radial artery catheters. Simultaneous samples of arterial (a) and mixed venous (mv) blood at rest, peak exercise, and one hour post-exercise were obtained from 10 patients with PAH (VO2max <85% predicted, Qmax <80% predicted, PAP >30 mmHg, and PVR >80 dyn s cm⁻¹) and 10 controls (VO2max and Qmax both >80% predicted). These were analyzed for [NOx] using chemiluminescence. Data are median [interquartile ranges]. Comparisons used the Mann-Whitney test.

Results: NOx flux increased from rest to exercise in controls (45%, [4, 77], p=0.02), but not in PAH (0%, [-27, 15], p=0.97).

NOx, increased in both groups (11% [2, 26] v 7% [7, 40], p=0.80). NOx flux (Qmax x (mv–a [NOx])) in controls was greater than PAH (370% [-100, 4869] v -96% [-460, 6], p=0.04).

There were no differences in [NOx] during recovery.

Conclusions: Normal pulmonary vasodilation and recruitment during exercise may be dependent on NOx bioavailability in mixed venous blood.

P2309

Comparing cardiac magnetic resonance imaging in group 1 and group 4 pulmonary hypertension

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Background and aim: Pulmonary arterial hypertension (PAH, group 1) and chronic thromboembolic PH (CTEPH, group 4) have different pathophysiology. Our study tested the hypothesis that PAH and CTEPH display different characteristics on cardiac magnetic resonance imaging (CMR).

Methods: 46 patients (mean age 54±15 yrs; 22F) entered the study, namely 23 PAH and 23 CTEPH matched for age and sex. They underwent right heart catheterization and cine and phase-contrast CMR (1.5 T scanner, Siemens) with arterial pressures. Patients were selected from a population referred to the MGH Cardiopulmonary Exercise Laboratory for invasive incremental cardiopulmonary exercise testing with pulmonary and radial artery catheters. Simultaneous samples of arterial (a) and mixed venous (mv) blood at rest, peak exercise, and one hour post-exercise were obtained from 10 patients with PAH (VO2max <85% predicted, Qmax <80% predicted, PAP >30 mmHg, and PVR >80 dyn s cm⁻¹) and 10 controls (VO2max and Qmax both >80% predicted). These were analyzed for [NOx] using chemiluminescence. Data are median [interquartile ranges]. Comparisons used the Mann-Whitney test.

Results: NOx flux increased from rest to exercise in controls (45%, [4, 77], p=0.02), but not in PAH (0%, [-27, 15], p=0.97).

There were no differences in [NOx] during recovery.

Conclusions: Normal pulmonary vasodilation and recruitment during exercise may be dependent on NOx bioavailability in mixed venous blood.

P2310

The indirect Fick method is an unfeasible method for hemodynamic assessment in pulmonary arterial hypertension patients

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The indirect Fick method (FickInd) is often used for the hemodynamic evaluation in Pulmonary arterial hypertension (PAH). As the FickInd calculates the cardiac output (CO) assuming physiological VO₂ values, this method might be unfeasible for patients with pulmonary vascular diseases. We evaluated the suitability of hemodynamic data obtained by FickInd in PAH.

Right heart catheterization was performed in 43 PAH patients (age 61±13 yrs) and 9 controls. 61% of patients suffered from idiopathic PAH, 30% from PAH associated with connective tissue diseases, the remaining 9% from other forms of PAH. Hemodynamic results obtained by FickInd were compared to data from the thermodilution (TD) method.

Patients and controls did not differ in age and BSA. No significant difference between heart rates during the different techniques was detected in either group. CO measured by FickInd (COFick) was 4.3±1.8 and 4.7±1.2 L/min in PAH patients and controls, respectively. In PAH patients CO by TD method (COThermo) was consistently higher than COFick (4.9±2.0 L/min) showing a significant difference (Wilcoxon; p<0.001). In controls COFick was 5.4±1.4 L/min (not significant to COFick). Agreement analysis of COFick and COThermo revealed a comparable bias between methods in both groups (0.5±1.1 L/min in patients; 0.65±0.82 L/min in controls) with wider limits of agreement for the patient cohort (-1.6 to 2.6 L/min versus -1.0 to 2.3 L/min in controls).

Determination of CO by the FickInd method cannot be used in PAH patients as this method consequently underestimates CO. It can be suggested that the estimated VO₂ values in use for the calculation of the CO are invalid for PAH patients.

P2311

Incapacity to increase pulmonary blood flow determines 6 minutes walking distance in pulmonary hypertension

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Introduction: Pulmonary hypertension (PH) is a disease of elevated pulmonary artery pressure leading to the inability of the overloaded right ventricle to adapt pulmonary blood flow (PBF) and systemic oxygen delivery to peripheral tissue oxygen demand. 6 minutes walk test (6MWT) is a submaximal, well tolerated but strenuous test regularly used for the assessment of PH functional status and is strongly associated to survival.

Aim: To study the adaptation of PBF during 6MWT.

Methods: We measured heart rate (HR) and PBF with a rebreathing device (INNOCOR) before and directly after a 6MWT in 28 patients with chronic thromboembolic pulmonary hypertension and 6 with pulmonary arterial hypertension.

The relation between increase (after – before 6MWT) in PBF (ΔPBF) in response to 6MWDistance (6MWD) was plotted and different mathematical model applied to describe the relation (Akaike test).

Results/Discussion: The best fitting model is a polynomial cubic model, showing a small and constant ΔPBF for patients walking less than 300-350 m but more rise in ΔPBF is observed with increased distance.

We notice that the rise in ΔPBF occurs at comparable 6MWD that is associated with better survival in PH. The stroke volume (PBF/HR) is not increased whatever the distance covered.

Conclusions: Ability to substantially increase PBF determines 6MWD and is dependent on chronicotropic response in patient with PH.
A lower resting heart rate may be prognostically favourable in pulmonary arterial hypertension
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**Background:** A resting heart rate (RHR) over 70 bpm is associated with increased mortality in left heart failure. We investigated the prognostic value of RHR in pulmonary arterial hypertension (PAH).

**Methods:** We related RHR during baseline right heart catheterisation from PAH-patients to their characteristics and outcomes.

**Results:** Data from 126 PAH (84 females, age 52±17y, 70 diopathic, 27 collagen vascular, 12 congenital heart, 13 HIV, 4 portopulmonal) catheterised from 2000 to 2010 were analysed. Patients were in NYHA II/III/IV (18/67/41), mean 6MWD 122 m, RHR 82±14 bpm, mPAP 49±17 mmHg, PVR 826±470 dyn*s*m-5, the mean follow-up was 46±35 month under optimal medical treatment. Patients with a RHR ≤ 70 bpm had a lower PVR 664±384 vs 887±487 dyn*s*m-5 but did otherwise not defer from a RHR > 70 bpm. 76% of patients with a RHR ≤ 70 bpm were alive after 58±37 months compared to 60% with a RHR > 70 bpm.

**Conclusion:** In this cohort we found that baseline RHR might be prognostically important in PAH. The role of RHR in PAH and whether reducing RHR in in analogy to left heart failure should be analysed in larger cohorts.

**P2313**
Effect of healthy ageing on alveolar-capillary recruitment during exercise
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Ageing is associated with deterioration in the structure and function of the pulmonary circulation with a decrease in alveolar-capillary surface area. We asked whether age-related changes in the pulmonary circulation limit alveolar-capillary recruitment and gas exchange during exercise in healthy older adults. 5 old (OLD; 66±8 yr, VO2max 140±31% age-predicted) and 8 young adults (YNG; 28±2 yr, VO2max 131±17% age-predicted) participated. Lung diffusing capacity for carbon monoxide (DLCO), cardiac output (Q), pulmonary capillary blood volume (Vc) and membrane diffusing capacity (Dm) were measured via a rebreathe method at rest and during cycle exercise at 25, 50, 75 and 90% of peak power. SaO2 was measured throughout exercise via pulse oximetry. At rest, DLCO, Vc, and Dm were lower in the OLD vs. the YNG group (22.3±3.8 vs. 20.6±4.7 ml/min/mmHg, 70±26 vs.102±48 ml, 35.2±7.9 vs. 46.6±12.3 ml/min/mmHg, P<0.05). However, DLCO increased linearly with exercise intensity in both groups with no plateau or change in slope in DLCO with increasing Q (Fig. 1). Vc and Dm also increased with progressive exercise in both groups (Fig. 1). SaO2 did not change during exercise in either group.

**Figure 1.** DLCO, Vc and Dm vs. Q in healthy old (OLD) and young (YNG) adults.

These data suggest that the age-associated changes in the pulmonary circulation do not impair alveolar-capillary recruitment and gas exchange during exercise in healthy older adults. NIH HL71478

**P2314**
Right heart volume load response in patients with chronic thromboembolic pulmonary hypertension (CTEPH)
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**Aim:** To assess the influence of volume load on right heart hemodynamics in pts with moderate and severe CTEPH.

**Patients and methods:** 20 patients (mean age - 47±11, 15 males and 5 females). The 1 group consisted of 9 pts with PAP ≤30 mm Hg, the 2 group – 11 pts with PAP>30 mm Hg. Right ventricular end-diastolic volume and ejection fraction were evaluated by thermodilution method [Lichtwarck-Aschoff, 2002].

**Results:** Results are summarized in the following table.

<table>
<thead>
<tr>
<th>Stages</th>
<th>PAP ≤30</th>
<th>PAP &gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDVI, ml/m2</td>
<td>1</td>
<td>115±15.1</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>2</td>
<td>145±16.1</td>
</tr>
<tr>
<td>CI, l/min/m2</td>
<td>3</td>
<td>37.4±2.75</td>
</tr>
<tr>
<td>PVRI, dyn s cm-5/m2</td>
<td>3</td>
<td>3.00±0.20</td>
</tr>
<tr>
<td>RVEDVI/C1/2 RVEF/1/2*PAP1/2</td>
<td>2/1</td>
<td>113±18.0</td>
</tr>
<tr>
<td>RVEF/C1/2 RVEF/1/2*PAP1/2</td>
<td>2</td>
<td>158±16.7</td>
</tr>
<tr>
<td>PVRI/C1/2 RVEF/1/2*PAP1/2</td>
<td>2/1</td>
<td>0.80±0.90</td>
</tr>
</tbody>
</table>

*Statistically significant (p<0.05) between groups.

After volume load: The difference in RVEDVI between the groups was not significant. The difference in CI between the groups became significant. This confirmed that there was no increase in CI in group 2. The increase of CI in group 1 was accompanied by PVRI rise. PVRI in group 2 remained high. Right ventricular end-diastolic volume and ejection fraction were evaluated by thermodilution method [Lichtwarck-Aschoff, 2002].

**Conclusion:** There were two main haemodynamic consequences in CTEPH: RV systolic dysfunction due to afterload increase and diastolic impairment as a response to volume load leading to RVEF decrease. The severity of right heart changes could be used in preoperative risk stratification in CTEPH patients.
Background and aim: In pulmonary hypertension (PH), the increased afterload leads to an increase in right ventricular (RV) myocardial oxygen demand. The RV mean systolic ejection pressure (Pms) and the RV systolic pressure-time integral (SPTI) have been proposed as valuable estimates of RV afterload and myocardial oxygen demand, respectively. Our study documented the correlates of Pms and SPTI in PH patients.

Material and methods: Eleven PH patients (mean pulmonary artery pressure mPAP = 57±10 mmHg) were studied, namely 6 arterial PH and 5 chronic thromboembolic PH. They underwent high-fidelity right heart catheterization at rest and on mild exercise (cycling) while supine. The workload was increased stepwise up to 60 W and to three-to-six hemodynamic points were obtained. The Pms was calculated as the pulmonary artery pressure (PAP) averaged over the systolic duration, i.e., from end-diastolic to dicrotic notch. The SPTI was the Pms times the systolic PAP pressure weighted by the systolic duration. The Pms matched 80% sPAP (bias = 0±2 mmHg). The SPTI ranged from 15.7 to 32.3 mmHg·sec and was related to PA pulse pressure (r²=0.80), sPAP (r²=0.67), mPAP (r²=0.46) and systolic duration (r²=0.22) (each P < 0.05).

Conclusion: In PH patients performing mild exercise, RV afterload (Pms) was related to the steady component of arterial load (mPAP, sPAP) while the RV myocardial oxygen demand (SPTI) was mainly related to the pulsatile component of arterial load (spiral PA pressure).

P2316

Effects of interval exercise on cigarette smoke-induced right ventricular dysfunction in mice

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Background: Right ventricular heart failure in COPD is thought to be a result of pulmonary hypertension due to increased pulmonary vascular resistance. Exercise, and especially interval training has been shown to be effective in improving left ventricular function, but the same is not shown for right ventricular function in COPD. The goal of this study was to examine the effects of aerobic interval training on cigarette smoke-induced right ventricular heart dysfunction in a mouse model for COPD.

Methods: 42 female A/J-OlaHsd mice were exposed to either cigarette smoke (CS) or fresh air (FA), for 14 weeks, 6 hours/day, 5 days/week. For the next four weeks they were either kept sedate (Se) or put through interval treadmill running (IT) for 1 hour/day, 5 days/week. After this period the mice were sedated with light isoflurane anaesthesia and the heart function was evaluated with echocardiography. Tricuspid annular plane systolic excursion (TAPSE) was used as a measurement of right ventricular function.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Mean VO2max (mL/kg0.75/min)</th>
<th>Mean TAPSE (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA-Se</td>
<td>32.1</td>
<td>0.71</td>
</tr>
<tr>
<td>FA-IT</td>
<td>40.5</td>
<td>0.82</td>
</tr>
<tr>
<td>CS-Se</td>
<td>32.9</td>
<td>0.46</td>
</tr>
<tr>
<td>CS-IT</td>
<td>41.6</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Maximal oxygen uptake was higher for the IT groups compared to the Se groups (p<0.05). TAPSE was reduced for the CS-Se group compared to all other groups (p<0.0001). There were no significant difference between the CS-IT group and the FA-Se group (p=0.35). The FA-IT group had significantly increased TAPSE compared to the FA-Se group (p<0.05), but not the CS-IT group (p=0.2).

Conclusion: Smoke exposure of A/J-OlaHsd mice causes a significant reduction in right ventricular function measured by echocardiographic TAPSE. This reduction seems to be normalized by intensive interval training.

P2317

Right ventricular diastolic stiffness in idiopathic pulmonary arterial hypertension

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Introduction: Idiopathic pulmonary arterial hypertension (iPAH) is a fatal disease with grim prognosis due to subsequent development of right heart failure (RHF). Findings in experimental pulmonary hypertension models suggest RHF is associated with increased diastolic stiffness.

Objective: This study investigates whether right ventricle (RV) diastolic stiffness is increased in iPAH patients.

Methods: Right heart catheterization (RHC) and MRI were performed in 28 patients suspected with iPAH. Based on pulmonary artery pressure, patients were divided into controls (7) and iPAH (21). Diastolic elasctance (diastolic stiffness), was quantified by the slope of diastolic pressure-volume relation, constructed by plotting RV end-systolic volumes and begin-diastolic pressures against RV end-diastolic volumes and end-diastolic pressures. Subsequently, we investigated whether diastolic elastance was associated with disease severity by comparing patients with lower RV stoke volumes (RVSV) and patients with higher RVSV.

Results: Diastolic elastance was significantly altered in iPAH (iPAH 0.25±0.04 vs Con 0.07±0.006, p<0.001). In addition, patients with lower RVSV had significantly higher diastolic elastance (LowRVS 0.05 ± 0.05 vs HighRVS 0.11±0.02).

Fig.1

Fig.2

Conclusion: This study demonstrates that RV diastolic stiffness is increased in iPAH patients and is associated with disease severity. In future studies we will investigate the prognostic relevance of these changes.
Abstract P2319 – Table 1. Echo parameters and NT-proBNP levels in PH and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PH ≤35m</th>
<th>CTD</th>
<th>SS</th>
<th>CORD</th>
<th>CHD</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAP, mmHg</td>
<td>94±5.3*</td>
<td>59±7.1*</td>
<td>55±6.7*</td>
<td>51±4.9*</td>
<td>71±8.2*</td>
<td>20±6.2*</td>
</tr>
<tr>
<td>NT-pro-BNP, mmol/l</td>
<td>1389±301.8*</td>
<td>1578±565.4*</td>
<td>931±619.3*</td>
<td>715±298.5*</td>
<td>512±235.9*</td>
<td>up to 334.0</td>
</tr>
<tr>
<td>Em h, sm/s</td>
<td>5.7±0.5*</td>
<td>6.4±0.7</td>
<td>7.1±0.7*</td>
<td>7.2±0.5*</td>
<td>7.0±0.5*</td>
<td>9±0.5</td>
</tr>
<tr>
<td>Em b, sm/s</td>
<td>5.7±0.6*</td>
<td>6.0±0.8*</td>
<td>7.2±0.8*</td>
<td>7.0±0.4*</td>
<td>7.0±0.6*</td>
<td>10.8±0.6</td>
</tr>
<tr>
<td>Em m, sm/s</td>
<td>5.0±0.6*</td>
<td>4.7±0.6*</td>
<td>5.7±0.7*</td>
<td>5.8±0.5*</td>
<td>5.0±0.6*</td>
<td>9±0.6</td>
</tr>
<tr>
<td>Em a, sm/s</td>
<td>3.2±0.5*</td>
<td>3.5±0.6*</td>
<td>3.9±0.5*</td>
<td>4.1±0.5*</td>
<td>4.0±0.5*</td>
<td>6.5±0.5</td>
</tr>
</tbody>
</table>

Tr, tricuspid ring; b, basal; m, medial; a, apical segment of RV. *p < 0.05 versus CG; † - PH ≤ 35 m, ‡ - CTD, § - SS, ‖ - CORD, ‡ - CHD pts.

P2319

263. Clinical features of pulmonary hypertension

P2320

Multislice CT angiography and pulmonary involvement in asymptomatic systemic lupus patients with antiphospholipid syndrome

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Objective: To detect the pulmonary involvement in asymptomatic secondary APS patients by pulmonary function tests (PFTs) and chest HRCT angiography and comparing the pulmonary findings to those of asymptomatic SLE patients without APS.

Patients and methods: Thirty-four SLE patients with APS and another 34 SLE patients without APS and with a negative ACE test were included as control. All patients were asymptomatic for any pulmonary manifestations. Plain chest x-ray, HRCT angiography and PFTs were performed for all patients in an attempt to assess the pulmonary vasculature and lung parenchyma. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) while assessment of organ damage was made using the Systemic Lupus International Collaborating Clinics /ACR (SLICC/ACR) index.

Results: There were abnormal pulmonary CT findings in 11 (32.35%) of the asymptomatic secondary APS patients with an obvious association to lupus anticoagulants. However, plain x-ray showed basal atelectasis and/or elevation of the copulae in 4 patients. Pulmonary abnormalities included a high frequency of pulmonary artery aneurysms (20.5%), thrombosis, basal atelectasis, embolism, bronchiectasis, pleural effusion and thickening. The SLEDAI and SLICC were significantly higher in APS patients. The PFTs including FVC, FEV1 and FEV1/FVC were reduced in APS patients compared to SLE patients only.

Conclusion: HRCT pulmonary angiography is useful in demonstrating the entire thoracic spectrum in asymptomatic APS patients. PFTs are reduced in SLE patients with APS compared to SLE patients only.

P2321

Thoracic affection during Behcet’s disease (about 15 cases)

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Behcet’s disease is a multisystem vasculitis that affects the young. Chest affection is rare and primarily venous. The arterial affection is exceptional. We report a retrospective study of 15 cases of Behcet’s disease with chest involvement, gathered at the Respiratory Diseases department, UHC Ibn Rochd of Casablanca from 1994 to 2010. It was about 3 women and 12 men. The average age was 34 years old (range: 19-58 years). The bipolar aphasisis was found in all patients, pseudo-ocularities in 9 cases, and hemoptyosis in 7 cases. Superior vena cava syndrome was noted in 8 cases, 6 cases of pleursy. The thoralorax showed bilateral pleursy in 1 case, unilateral in 5 cases, bilateral hilar opacities projection in one case, an alveolar opacity in 3 cases, aspect of releasing balloons in one case, and it is normal in 4 cases. The chest angio-CT showed the superior vena cava’s thrombosis in 9 cases, bilateral pulmonary arterial aneurysms in 2 patients, pulmonary artery aneurysm associated to an embolism in one patient and pulmonary infarction site in 3 cases. Echocardiography showed an intracardiac thrombus in one case. All patients were administered steroids, colchicine and anti-coagulants. Immunosuppressive drugs were administered for 3 patients. The evolution was good in 11 cases, the onset of neuro-Behcet in 1 case and we deplore 4 deaths due to a lightning hemopty. We emphasise throughout these series the scarcity of thoracic manifestations of Behcet’s disease, namely the arterial disease that makes its prognosis dull.

P2322

Prevalence of hepatopulmonary syndrome in candidates for liver transplantation in Santa Casa Hospital (Porto Alegre-Brazil)

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Background: Hepatopulmonary syndrome (HPS) is a disorder of pulmonary vascular disease secondary to liver disease, comprehending abnormalities of arterial oxygenation (PaO2 < 80 mmHg or alveolar-arterial oxygen gradient (PA-aO2) ≥ 15 mmHg on room air) and in larger 64 years PaO2 < 70 mmHg or PA-aO2 ≥ 20 mmHg and presence of pulmonary vascular dilatation. There are reports of its occurrence between 4-32% of cirrhotic liver transplant candidates. It is presence, independently and significantly, increases mortality and reduces the survival rate of those patients when compared with cirrhotic patients without HPS.

Objective: To assess the prevalence and severity of HPS in patients with severe liver disease.

Methods: Retrospective cross sectional review of 90 medical records of 90 patients who underwent liver transplantation at the Santa Casa Hospital (Porto Alegre -Brazil), from February 2002 to April 2009. The present study was approved by the Hospital Ethics Committee.

Results: The sample consisted of 90 patients, 62.2% (n = 56) were male and mean age was 54.13 years (22-74). The prevalence of HPS was 43.3% (n=39). Forty one per cent (n=16) were classified as having mild HPS, 33.3% (n=13) moderate, 10.3% (n=4), severe and 15.4% (n = 6) as very severe. The mean PaO2 was 62.42 mmHg and the mean PaO2 was 81.47 mmHg. The mean PA-aO2 was 10.3% (n=4), severe and 15.4% (n = 6) as very severe. The mean PaO2 was 26.42 mmHg and the mean PaO2 was 235.9 mmHg. The mean PA-aO2 was 7.1*ˆ and 55.67 mmHg. The mean PA-aO2 was 4.9*ˆ and 71.9 mmHg. The mean PA-aO2 was 2.3* and 71.9 mmHg.

Conclusion: The study confirms the high prevalence of this clinical syndrome in patients with severe liver disease and, thus, strengthen its research in patients with liver diseases, especially those who may be liver transplantation, since current evidence points to liver transplantation as a treatment of HPS.

P2323

WITHDRAWN
P2324 Pulmonary hypertension in patients with infective endocarditis
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Aim and methods: To study pulmonary hypertension (PH) in infective endocarditis (IE) pts with different localization, valve injury and activity of disease we have investigated 136 pts with native valve IE, in which 105 (76%) had left and 31 (25%) – sided IE. Diagnosis of IE was made according to Duke-criteria (ECS, 2009). Pulmonary artery systolic pressure (PASP) was measured using trans-thoracic EchoCG in dynamics taking into account the systolic tricuspid gradient and right atrium pressure.

Results: PH was revealed in 132 pts with IE (97%). Mean PASP was 53.7±16.2 mmHg. Pts with minimal and moderate PH prevailed (1st degree PH in 61 pts (45%), 2d degree – in 50 pts (37%), only 15% pts (21) proved high degree PH (PASP > 70 mmHg). No significant differences of PH level were found depending on the gender, age, left or right-sided localization of IE, acute stage or 1-year or more advanced stage of disease duration. Nevertheless the PH degree was significantly higher in the group of pts with bi-valve or multiple valve injury in comparison with group of pts with mono-valve pathology (61.3±15.8 vs 49.3±14.9, p<0.001). Among haemodynamic factors influencing the PASP most possible were left atrium diastolic size (R=0.556386, p=0.00001) and myocardium mass index (R=0.47, p<0.0001).

Conclusions: So PH naturally develops in pts with IE and haemodynamic factors proved to be most significant in its development.

P2325 Which patients with pulmonary arteriovenous malformations are dyspnoeic?

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Methods: To identify factors contributing to dyspnoea, a retrospective analysis of a single-centre 2005-2010 cohort 815 patients were included. The 55-center, observational, US Registry to Evaluate Early And Long-term pulmonary arterial hypertension (iEVAL) Disease Management (RE-VEAL) examines demographics, clinical course and management of patients (pts) diagnosed with PAH.

Results: 3518 pts enrolled in REVEAL between 03/2006 and 12/2009; 77 APAH-CHD and 122 IPAH/FPAH had childhood-onset PAH; mean ± SD age at PAH diagnosis 6.6±6 years and 9.6±6 years (P = 0.002), respectively. APAH-CHD had similar functional class (FC) at diagnosis compared with IPAH/FPAH (FC: I, 5%; II, 51%; III, 32%; and IV, 11% vs FC: I, 7%; II, 40%; III, 43%; and IV, 10%, respectively; P = 0.64). Hemodynamics were also similar at diagnosis. Similar proportions were treated with endothelin receptor antagonists (APAHP-CHD, 40% vs IPAH/FPAH, 45% vs P = 0.53), though phosphodiesterase 5 inhibitors (45% vs 64%, respectively; P = 0.011) and prostacyclin (28% vs 50%, respectively; P = 0.003) analogs were used less in APAH-CHD. Five-year survival from diagnosis was similar for APAH-CHD and IPAH/FPAH (71.1±4% vs 75.0±7% vs, respectively; P = 0.53).

Conclusion: Childhood-onset APAH-CHD and IPAH/FPAH have similar hemodynamics and FC and similar 5-year survival from diagnosis. REVEAL provides observational data on treatment and outcomes in childhood PAH that should prove useful in identifying prognostic parameters, thereby helping clinicians improve outcomes.
Background: The prevalence of pulmonary hypertension (PH) has been estimated to 6.7% in 95 patients with lymphangioleiomyomatosis (LAM) as defined by sPAP>35 mmHg at echocardiography.

Objective: To evaluate the hemodynamic characteristics and pulmonary function in patients with LAM and PH not explained otherwise.

Methods: A retrospective multicenter study was conducted in patients with LAM with PH or PH associated with diffuse pulmonary involvement. 25 mmHg, pulmonary artery wedge pressure (<15 mmHg, and normal or decreased cardiac index at RHC).

Results: Twenty patients were studied, with a mean age of 49±12 years. The median delay between the diagnosis of LAM and PH was 6.2 years. Dyspnea was NYHA class III in 10%, III in 50%, and IV in 46%. A single patient had right heart failure. Six minute walk distance was 340±84 m. Hemodynamic characteristics were: mean PAP 32.6±6 mmHg, cardiac index 3.5±1.1 L/min.m², pulmonary vascular resistance (PVR) 376±184 dyn.s.cm⁻⁵, and pulmonary capillary wedge pressure 10.3±3 mmHg. The mean PAP was >35 mmHg in 3 cases, FVC was 76±28% of predicted, FEV1 42±7, P(125) 1.3 kPa on room air. All patients were on long-term oxygen therapy. In five patients receiving bosentan, RHC after a median of 3.2 years demonstrated a median decrease of 42% in PVR. After a median follow-up of 2.9 years, one patient had died of cardiac arrest, and 5 patients had undergone lung transplantation.

Conclusion: Prevalence of PH may be higher in patients with LAM and severe pulmonary function impairment. Bosentan therapy might improve hemodynamic characteristics.

Support: CNMIR and FP7 of the European Commission.

P2328 Pulmonary hypertension in lymphangioleiomyomatosis: Hemodynamic characteristics in a series of 20 patients
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Doppler-echocardiogram in 35 SLE patients. The average duration of SLE in these patients was 14±6.1 years. A control group consisted of 20 healthy persons.

Results: There was no significant difference between the initial diameters of brachial artery in SLE (3.35±0.06 mm) and SLE-PH groups (3.43±0.09 mm) compared with control group (3.46±0.07 mm). The significant reduction of EDV/DV on 34% in SLE patients compared to healthy persons was determined in the test with P=0.04. Abnormalities of endothelium dependent vascular tone regulation in patients with PH were more expressed (reduced on 48% compared with healthy persons) (p<0.05). At the same time EDDV in SLE group without PH and in control group did not differ, but in SLE-PH patients the EDDV was 1.6 times less compared with control.

Conclusion: Abnormality of EDV/D is dominated in SLE patients. The most evident disorder of EDV occurs in SLE patients during the PHA progress. In patients with PHA also noted reduction of vasoregulation function of smooth-muscular cells, because they had impaired EDDV.
P2333

Prevalence of pulmonary arterial hypertension in the HIV cohort of the University Bonn: Results of the PAHIBO study

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Background: PAH (pulmonary arterial hypertension) is a rare and life-threatening complication of HIV (human immunodeficiency virus) infection. An investigation of the presence of HIV infection is a standard diagnosis in patients with unexplained PAH. Previous studies suggest a prevalence of PAH in HIV patients close to about 0.5%, but are limited in the study design. Therefore the exact prevalence is unclear.

Methods: The PAHIBO study is investigating all HIV patients (n = 700) at the University Hospital of Bonn in a prospective cross-sectional study. If systolic pulmonary arterial pressure (sPAP) is > 35 mmHg in Doppler echocardiography, right heart catheterization is followed.

Results: Of 700 patients enrolled, 443/340 (13%) had an echocardiographic sPAP > 35 mm Hg. The right heart catheterization was carried out so far in 22/44 patients with echocardiographically proven PH. In 4 cases, a precapillary PAH (including a complete work-up and exclusion of other causes of PAH) was diagnosed, of which 1 case was already known, in 13 cases postcapillary PH and in the remaining 5 cases, the exclusion of a manifest PH. Thus, the PAHIBO study reveals a prevalence of HIV-associated PAH of at least 4/340 cases (1.2%).

Conclusion: The prevalence of HIV-associated PAH is probably higher than previously described. Severe cardiac and respiratory comorbidities are very frequent in the examined HIV cohort. If these results should be confirmed in the extended cohort of 700 patients, a regular echocardiographic screening in asymptomatic HIV patients is to discuss.

P2334

Characteristics of PAH associated with pretricuspid shunts in the French PAH registry

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The diagnosis of pulmonary arterial hypertension (PAH) associated with pretricuspid shunts (PTS) is often made in adulthood. The characteristics of this subgroup of CHD PAH are not well established.

Objective: To review and analyze patients with PAH and PTS enrolled in the second prospective French PAH registry, initiated in 2006.

Results: Of 1524 patients enrolled in the registry, 81 patients with PAH and PTS were identified. The diagnosis of PAH was made after the diagnosis of CHD, in 70% of cases. PAH appeared during the follow-up of the CHD in 28% of cases. At inclusion, 5% were in functional class (FC) IV, 61% were in FC III and 34% in FC I or II. 6MWD was 360±107m. Pulmonary hemodynamics were: mPAP=53±11mmHg, CO=5.0±1.7L/min and PVR=11±8.3WU. 50% of patients in FC I or III received PAH specific therapy. During the 3-year follow-up period, 9 patients died and 3 underwent heart-lung transplantation.

Conclusion: In this registry, the proportion of CHD-PAH due to PTS compared to other forms of CHD is higher than in previously reported series. The natural history of PTS remains poorly understood as PAH can be diagnosed throughout life. PAH specific therapies are not widely used in the PAH associated with PTS population.

P2335

Health-related quality of life in patients with pulmonary arterial hypertension

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Introduction: Although many epidemiological data of primary Pulmonary Hypertension (PH) have been recorded, the literature as regards the characteristics of the general population suffering from PH is nevertheless scarce.

Aim: To determine the clinical characteristics of the different types of PH in a cardiologist service of a general hospital patients.

Results: 204 out of the 321 patients evaluated from January 1994 to December 2009 met the inclusion criteria. The average age was 73,36±17,48 years old, 55% of whom were women. The average initial PSAP was 74±8,2 mmHg. The predominant type found was PH owing to left heart disease 88 cases (43,3%), the most common etiology being mitral valve pathology (53/87). Pulmonary arterial hypertension (PAH) represented 23% of the overall, there being ten cases of hypoxemia right shunts, four cases of primary PH, a case of seleroderma, another one of anorectics and two cases of portal hypertension. In eleven cases (13%) PH was associated with respiratory disease while the remaining 13% corresponded to PH caused by chronic thromboembolism. An overall worse prognosis compared to other ethnic groups.

Conclusion: The clinical characteristics of the different types of PH in a cardiologist service of a general hospital patients.
P2338
Survival and prognostic factors in patients with incident systemic sclerosis-associated pulmonary arterial hypertension from the French registry
David Lamy1, Olivier Sibot2, Jean-François Corder2, Eric Hachulla1, Luc Mouton3, Virginie Gressan1, Laurence Rottat1, Pierre Clerson1, Gérard Simonneau1, Marc Humbert1. 1French National Reference Centre of the French PAH Registry; 2Internal Medicine, Claude-Huriez Hospital, Lille, France; 3Respiratory Medicine, Antoine-Beclere Hospital, Clamart, France. Aims and objectives: This study describes the characteristics and outcome of SSc patients enrolled in the multicentric French PAH registry since 2006.
Methods: SSc patients enrolled in the registry between January 2006 and November 2009 were prospectively included if they had PAH diagnosed within 1 yr prior to enrollment (incident patients). Patients with interstitial lung disease (ILD) were included if forced vital capacity (FVC) >70%.
Results: 91/145 SSc patients were included; 81% were in NYHA III or IV. Mean pulmonary arterial pressure (mPAP) was 40±10 mmHg, mean cardiac index was 2.6±0.8 L/min/m2 and mean pulmonary vascular resistance (PVR) was 670±351 dyn sec cm-5. Overall survival was 90%, 76% and 54% at 1, 2 and 3 years, respectively. Male gender (HR: 2.44, age (HR: 1.044), desaturation after 6-minute walk test (HR: 0.93), PaO2 (HR: 0.96) and cardiac index (HR: 0.52) were factors prognostic of survival. Other parameters did not reach statistical significance, including NYHA, PVR, 6MWD, BNP, DLCO/VA and mPAP.
Conclusions: These results confirm the poor prognosis for incident SSc-PAH patients even in the modern era. As with idiopathic PAH, gender and age appear to be important prognostic factors. Cardiac index, but not mPAP, had a significant impact on survival. For the first time, PaO2 at rest and desaturation during exercise were shown to be significant prognostic factors in SSc-PAH.

P2339
Right axis deviation is a strong indicator of pulmonary hypertension in a risk population
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Pulmonary hypertension (PH) is diagnosed by right heart catheterization (RHC), but non-invasive methods play an important role in screening and follow-up. ECG is routinely performed in the clinical work-up but its clinical value has not been defined. We hypothesized that a simple parameter, such as the presence of right axis deviation (RAD) in standard ECG might be useful in the diagnosis and follow up of PH.
We retrospectively analysed all patients who received a RHC and an ECG in our department between 2005 and 2010. The indication for RHC was heterogeneous, the pretest probability of PH was about 50%. We determined the ratio of the S and R waves in lead I in each patient, a value ≥1 (≥90°) was considered as RAD. The investigator was blinded to the RHC results. The sensitivity and specificity of RAD to predict PH (mean PAP>25mmHg) was determined.
N=317 patients were included. RAD was present in n=71 patients. Within these, PH was detected in n=65 patients, and was missing in n=6 subjects (p<0.001). In n=246 patients without RAD, PH was present in n=87 patients. The specificity of RAD for PH was 96%, whereas the sensitivity was merely 43%. Accordingly, the positive predictive value of RAD to predict PH was 92%, while its negative predictive value to rule out PH was just 35%.
Our retrospective analysis on a large, heterogeneous cohort of subjects including patients with and without PH suggests that the presence of RAD in the ECG has a high specificity but a low sensitivity for PH. This simple method may help to recognize PH patients within a population at risk for PH. In order to determine its appropriate role in a diagnostic algorithm, prospective, population based studies are needed.

264. Clinical features of pulmonary thromboembolism
P2340
A radiological grading system for risk stratification of acute pulmonary embolism: A pilot study
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Introduction: There is currently no radiological scoring system for Pulmonary Embolism (PE) and studies suggest such a system may provide risk stratification data.
Null hypothesis: Radiological severity grading of PE has no prognostic information.
Methods: All CT Pulmonary Angiograms (CTPAs) over a 6-month period were analyzed and demographic data collected. A radiologist graded all positive CTPAs, into mild, moderate and severe according to agreed criteria. Variables including: troponin; D-Dimer; CRP; length of in-patient stay; mortality data and re-admissions secondary to PE were recorded.
Results: 312 CTPAs were performed: 240 were negative (76.9%) and 72 patients had a PE (23.1%). In the PE group, 21 were male (29.2%); 51 female (70.8%) and the average length of in-patient stay was 19 days. This was significantly longer in the moderately/severe group than mild (p=0.01). There is no correlation between RV dimension and severity of PE. D-Dimer and troponin increase with radiological severe PE but is not statistically significant. More patients with radiological severe PE are re-admitted (13.6%) compared with mild/moderate group (5.32%), however samples were insufficient for analysis, as was the mortality data.
13.9% of CTPAs had the diagnosis changed or disputed. 60.4% negative CTPAs had no D-Dimer collected; 40.9% had an alternative diagnosis to PE.
Conclusions: This study suggests PE affects 2.4x more females than males and radiological severe PE is associated with longer in-patient stay and greater re-admissions. An adequately powered, prospective study of positive CTPAs is needed to further evaluate use of this grading system.

P2341
Correlation of levels of N-terminal pro-B-type natriuretic peptide with localization of thrombus in acute pulmonary embolism
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Aim: Brain-natriuretic peptide (BNP) is a hormone which is released from the heart. The aim of the study was to investigate whether N-terminal pro-BNP (pro-BNP) could predict localization of thrombus in patients with acute pulmonary embolism.
Method: The patients who were evaluated in emergency department, who had thrombus on helical computed tomography were enrolled. Thrombi which were localized on main/right-left pulmonary artery were classified as central, ones which were present at segmentary/subsegmentary levels as peripheral. Echocardiogram was performed and pro-BNP levels were measured.
Results: Forty-nine patients were enrolled to the study. The thrombi of 63.3% patients were unilaterally located, of 36.7% bilaterally, 18.4% of patients had thrombi that were central, 81.6% patients had peripheral. The difference between pro-BNP levels of who had central and peripheral thrombus was significant (p=0.039).

Pro-BNP levels of patients who had right ventricle overload (p<0.001, p=0.003, p=0.003). The pro-BNP levels of patients who were followed up in intensive care unit, needed trombolytic treatment were higher (p<0.001, p=0.002).
Conclusion: Higher pro-BNP levels indicates higher probability of more central location of thrombus, resulting adverse clinical course and having right ventricular overload.
P2342
Pulmonary thromboembolism during acute chest syndrome in sickle cell disease
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Background: Although pulmonary infarction and pulmonary embolism (PE) have been reported in sickle cell disease patients during acute chest syndrome (ACS), there is no comprehensive study evaluating the prevalence of PE during ACS.

Methods: We screened 123 consecutive patients during 144 ACS episodes to perform a multidetector computed tomography (MDCT). 121 MDCTs (in 103 consecutive patients) were included in the study.

Findings: 20 MDCTs were positive for PE, determining a prevalence of 17% (95% confidence interval from 10% to 23%). Revised Geneva clinical probability score was similar when comparing patients with PE and those without. D-dimers testing was very often positive (95%) during ACS. A precipitating factor for ACS was less frequently found in patients with PE as compared to those without. Patients with PE exhibited significantly increased platelet counts (517 [273-729] vs. 307 [228-412] μL/L, p<0.01) and smaller bilirubin peak (36 [18-51] vs. 46 [32-83] μmol/L, p=0.048) and lactate dehydrogenase peak (537 [320-704] vs. 604 [442-788] IU/L, p=0.01) during hospital stay as compared to others. In addition, patients with PE had a higher platelet count peak (537 [345-785] vs. 417 [330-555] 10^9/L, p=0.048) and smaller bilirubin peak (36 [18-51] vs. 46 [32-83] μmol/L, p=0.048) and lactate dehydrogenase peak (537 [320-704] vs. 604 [442-788] IU/L, p=0.01) during hospital stay as compared to others.

Interpretation: PE is not a rare event in the context of ACS and seems more likely in patients with higher platelets counts and lower haemolytic rate during ACS. SCD patients presenting with respiratory symptoms suggestive of ACS may benefit from evaluation for PE.

P2343
The sensitivity of D-dimer testing versus multislice CT in the diagnosis of postpartum pulmonary embolism in symptomatic high risk women
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Background: Early detection of postpartum pulmonary embolism is a corner stone in prevention of its associated maternal mortality

Patients and methods: We applied d-dimer testing and Multislice CT scanning in prevention of its associated maternal mortality.

Results: Of 2359 cases, 60 cases (2.54%) were considered clinically highly suggestive of pulmonary embolism. Clinical parameters highly suggestive of pulmonary embolism were dyspnea (85%), overweight (51%), tachypnoea (55%) and lactate dehydrogenase peak (537 [320-704] vs. 604 [442-788] IU/L, p=0.01) during hospital stay as compared to others. In addition, patients with PE had a higher platelet count peak (537 [345-785] vs. 417 [330-555] 10^9/L, p=0.048) and smaller bilirubin peak (36 [18-51] vs. 46 [32-83] μmol/L, p=0.048) and lactate dehydrogenase peak (537 [320-704] vs. 604 [442-788] IU/L, p=0.01) during hospital stay as compared to others.

Interpretation: PE is not a rare event in the context of ACS and seems more likely in patients with higher platelets counts and lower haemolytic rate during ACS. SCD patients presenting with respiratory symptoms suggestive of ACS may benefit from evaluation for PE.

Conclusions: Postpartum d-dimer testing in patients showing suggestive symptoms of pulmonary embolism is not suitable for exclusion test, yet a strong screening tool.

P2344
Genetic mutations in Turkish population with pulmonary embolism and deep venous thrombosis
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Venous thromboembolism (VTE) is an universal health hazard throughout the world. Pulmonary embolism (PE) along with deep venous thrombosis (DVT) is a major clinical manifestation of VTE and inherited and acquired risk factors in-crease the risk. We aimed to evaluate the relationship between factor V (G1691A, A1090G, and A1299G), prothrombin (PT G20210A), methyleneetahydrofolate reductase (MTHFR C677T) mutations, plasminogen activator inhibitor 1 (PAI-1 4G/5G) polymorphisms, and VTE in Turkish population. Between years 2005-2009, 80 Turkish patients diagnosed with PE and PE+DVT and 104 controls at our institution and agreeing to participate, were consecutively recruited in the study. Heterozygous factor V Leiden (FVL) mutation was significantly higher among patients (p = 0.04) with allele frequency of 6.3% (p = 0.1). Heterozygous PT G20210A mutation was also significantly higher among patients (p=0.001) with allele frequency of 6.9% (p =.003). MTHFR 677TT genotype was significantly higher in patients (p =0.09) with allele frequency of 23.8% (p = 0.05). No significant difference was found in FV A1090G and FV A1299G mutation rate as well as PAI-1 genotypes and their allele frequencies (p > 0.05). Thus, frequencies of FV G1691A, PT G20210A, and MTHFR C677T mutations are higher in patients with VTE. FV A1090G, FV A1299G mutations, and PAI-1 gene polymorphisms may not be a risk factor for VTE in Turkish population. However, further follow-up evaluation in larger, multi-center series is required to examine the role of these genetic mutations as a risk factor for VTE in Turkish population.

P2345
Does anatomic location of deep venous thrombosis affect the clinical findings and course in the patient of pulmonary embolism
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Aim: Deep venous thrombosis (DVT) in proximal veins carries a significantly higher risk of pulmonary embolism (PE) than in distal veins. However, the effect of DVT anatomic location on clinical findings and course of PE is not known. We, therefore, investigated whether anatomic location of DVT could affect the clinical findings and course of PE.

Methods: Data of 81 patients diagnosed as PE between 2007-2011 were evaluated retrospectively. The patients were divided into two subgroups as proximal (saphenous, femoral, iliac veins) and distal disease (popliteal, crucial veins) according to DVT anatomic location. The patients with and without DVT, and also the subgroups of DVT were compared in respect of any symptom, clinical or laboratory findings evaluated.

Results: Doppler USG of 72 patients showed that 26 (36.1%) had no DVT, 29 (40.3%) proximal, and 17 (23.6%) distal disease. Dyspnea were more common (p=0.036) and mean PaO2; were significantly lower (p=0.022) in the patients with DVT than without DVT, while there were no significant differences between two groups in respect of PE clinical severity, hospitalization mortality, mortality rate, echocardiographic and laboratory findings.

Conclusions: This study showed that the patients with PE had more common rate of dyspnea symptom and hypoxemia in DVT existing than without DVT, however, anatomic location of the thrombosis did not affect the clinical findings and course of PE.

P2346
Prognostic value of two clinical scores in patients with acute symptomatic pulmonary embolism
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Introduction: Clinical models may accurately identify patients at low risk of overall death in the first month after diagnosis of PE; such patients might benefit from an abbreviated hospital stay or outpatient therapy. The aim of our study was to compare two scores (Spanish and PESI simplified-PESIs- scores) in an external cohort of patients with PE.

Methods: Patients from two Spanish hospitals diagnosed with acute symptomatic PE were consecutively included. The primary study outcome was 30-day overall mortality. The secondary outcome was a composite endpoint based on 30-day mortality or recurrent thromboembolism or major bleeding. We calculated the sensitivity, specificity, Predictive values and Likelihood ratios in both scores for primary and secondary outcomes. Receiver-operating characteristic (ROC) curves were assessed for both scores.

Results: The study included 1574 patients.861 were women (58%). The mean age was 67 years. The Spanish score classified 59% of patients at low risk and PESI scores only 29%. The NPV was significantly higher for PESI scores scaling considerate primary and the secondary outcomes. There was no significant differences in the area under the curve of both scores.

Conclusions: Sensitivity results in both scores are higher but PESI scores is slightly superior to Spanish score. PESI scores would have more acceptability due to better sensitivity and easy applicability.
Introduction: Right Ventricular Dysfunction (RVD) is a predictor of mortality in Pulmonary Embolism. The reproducibility of classic parameters is low. The TAPSE is easier and more reproducible.

Aim: To assess whether TAPSE has prognostic value in patients with PE.

Methods: PROTECT is a multicentric study of patients with hemodynamically stable PE; evolution data were gathered through 30 days. Echocardiography in the first 48 hours. RVD criteria: 1) RVEDD > 30; 2) RVLV > 1.3; 3) hypokinesia subjectively evaluated; or 4) TR jet > 2.8 m/s. Statistical analysis with SPSS (v. 15). Means were compared with T-Student for quantitative variables; Chi-square for qualitative. OR and corresponding 95CI calculated with univariate logistic regression. Multivariate analysis could not be carried out due to the low number of events.

Results: The study included 630 patients. Global mortality was 3.8%, and mortality due to PE was 0.8%. TAPSE could be determined in 91.7% of the patients. TAPSE ≤ 15 was associated with mortality (OR: 1.95; CI: 1.3-2.8).

Conclusions: TAPSE ≤ 15 is associated with mortality in PE patients. TAPSE may be used for the defining RVD which has prognostic importance in PE.

P2348
Incidence of chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism
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Background: Recent studies suggest that chronic thromboembolic pulmonary hypertension (CTEPH) following acute pulmonary embolism (PE) may be more common than previously thought.

Objective: To investigate the incidence of CTEPH and associated risk factors through a systematic screening in patients after acute PE in China.

Methods: A cohort study of consecutive patients with acute PE in a national referral institute was retro and prospectively approached by a questionnaire for the presence of new or increased complaints of dyspnea after acute PE episode. Subsequently, these patients were evaluated for the presence of pulmonary hypertension with echocardiography, perfusion lung scanning and right heart catheterization (RHC) in follow-up period. Pulmonary hypertension was defined as a systolic pulmonary artery pressure ≥ 50 mmHg at rest in the presence of residual perfusion defects at perfusion lung scanning.

Results: From 2006 to 2010, 488 patients with acute PE were screened, and 475 patients were included. Overall mortality after a median follow-up period of 21 months was 12.9%; 74 patients were lost to follow-up. In the remaining patients, nine were diagnosed with pulmonary hypertension by echocardiography, and two of the nine patients underwent right heart catheterization (RHC). The incidence of CTEPH after acute PE was 2.24%. The incidence of CTEPH after acute PE was 2.24%. In Cox regression, 173 cases which had missing data of biomarkers were involved. The analysis showed that protein C deficiency (hazard ratio, 10.40, 95% confidence interval, 1.06 to 102.25) increased the risk of CTEPH after acute PE.

Conclusions: The incidence of CTEPH after acute PE was 2.24%. Protein C deficiency may increase the risk of CTEPH.

P2350
Association between right ventricular dysfunction and diameter of right descending pulmonary artery on chest X-rays in pulmonary embolism
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Background: Incidence of CTEPH following idiopathic PE has been reported as 4%. The British Thoracic Society (BTS) recommends that patients with massive or submassive PE should undergo echocardiography 6-12 weeks following the index event. Aims: To investigate local practice in the follow-up of patients with acute PE to devise management guidelines.

Methods: A retrospective study of 110 patients diagnosed with acute PE at our hospital between 2007 and 2008 was conducted. Mean age was 68.6 years (range 27-100), 40 (36%) were males and 18 (16%) had previous venous thromboembolism. In 51 (46%) patients PE was idiopathic.

Results: All patients diagnosed with PE were normotensive and 27 (25%) had in-patient echocardiography (ECHO). In 5 (18%) patients scan confirmed RV dilatation and 2 of them had repeated ECHO within 2 months. Subsequently one patient was diagnosed with CTEPH and underwent pulmonary endarterectomy. In the group of patients with acute PE but without in-patient echocardiography, 40 (83%) received a follow-up appointment (mean 4 months) and 10 (25%) had follow-up ECHO. Two more patients were diagnosed with CTEPH during this period (mean 34 months) with an overall incidence of 2.9%.

Conclusion: Record outcome, literature review and the BTS/ERS guidelines resulted in the development of local protocol for the screening acute PE survivors for CTEPH.

P2366
Dilated cardiomyopathy: an update of diagnosis and management
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Chronic thromboembolic pulmonary hypertension associated with Klippel–Trenaunay syndrome: A retrospective series of 5 patients

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Introduction: Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder characterized by the triad: (1) cutaneous capillary malformations; (2) soft tissue and bone hypertrophy; (3) multiple vascular malformations at arteriolar, venous and lymphatic level. KTS is associated with recurrent venous thromboembolism (VTE), that may lead to chronic thromboembolic pulmonary hypertension (CTEHP).

Patients and methods: We retrospectively reviewed clinical and haemodynamical characteristics of 5 patients with CTEHP associated with KTS referred to our center between 1993 and 2010.

Results: Four patients had a previous history of VTE. At diagnosis, 1 patient was in NYHA Functional Class (FC) II and 4 patients were in NYHA FC III. Pulmonary haemodynamics were: mean pulmonary artery pressure (mPAP)=56.4±9.4 mmHg. Cardiac index (CI)=2.74±0.89 l/min/m² and total pulmonary resistance (TPR)=20.2±12.4 Wood units. One patient had proximal CTEHP, underwent a pulmonary endarterectomy and normalized his pulmonary pressures after surgery. The other 4 patients had inoperable CTEHP due to distal lesions and were treated with specific pulmonary arterial hypertension (PAH) therapy. Two patients were clinically and haemodynamically improved by oral therapy with a mean reduction of 22% of the mPAP and 60% of the TPR after a mean follow-up of 50 months. One patient died during 34 months due to recurrent VTE complications and one patient needed a heart–lung transplantation after 15 years of follow-up.

Conclusion: CTEHP is a rare but severe complication of KTS. Careful monitoring of patients with KTS in a multidisciplinary setting is thus appropriate.

Clinical research of central and lung hemodynamics in patients with pulmonary thromboendarterectomy (PTEA)

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The aim of study: to find factors have influence on patient condition after pulmonary thromboendarterectomy (PTEA).

Patients and methods: 13 patients with chronic pulmonary lung thromboembolism (CLT) were enrolled in prospective study. Invasive lung and systemic hemodynamic monitoring was performed after induction of anesthesia before the operation using PICCO PLUS and VOLEF device. Arterial blood samples were taken at the same time.

Results: All patients had:
- Cardiac volume changes: reduction of global end-diastolic volume index less than 680 ml/m², extension of right ventricle end-diastolic volume index more than 195 mm², correlation between right and left heart volume was 2:1
- Extravascular lung water index was more than 11 ml/kg, lung vessels permeability was not heightened significantly
- Contractility was decreased: cardiac output (CI) index less than 2.50/min/mm², left ventricle contractility index (dP/dx) less than 1000 mm Hg, right ventricle ejection fraction less than 14%
- CI and dP/dx was beyond above in second group
- Right ventricle afterload was raised significantly: Pulmonary vascular resistance varied from 250 to 2500, mean 1350
- Pulmonary and systemic vascular resistance ratio was 1:1.28 in first group and 1:3.19 in 2nd group.

Conclusions: Patients with CLT have specific hemodynamic changes. Reduction of contractility and increase of afterload may have an influence to development of reperfusion lung edema supplementary study is necessary to expose factors estimated surviving after PTA.

Incidental findings on computer tomography pulmonary angiograms, a UK district general hospital’s experience

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Background: CTPA is 1st line imaging of suspected pulmonary emboli (PE) in UK hospitals.

Aims and objectives: CTPA yields 3D images of thoracic and upper abdominal organs, thus detects unanticipated diagnoses termed “incidental findings” (IF). We investigated the nature of IFs on CTPAs done at Dorset County Hospital.

Methodology: All CTPA reports from October-09 to March-10 were retrospectively reviewed, noting diagnosis of PE (positive CTPA), additional findings, particularly IFs, validated against previous imaging reports.

Results: Total CTPA reports were 490 (51% males) PE was diagnosed on 113 (23.6% ± 3.73%, 95% CI). Total additional findings were 781. Mean additional findings per CTPA was 1.6±0.11 (95% CI). Total IFs were 515, 335 of pulmonary origin (63.05% ± 4.66%, 95% CI), including pleural effusions (81%), consolidation (46%), emphysema (36%), and collapse (35%); pulmonary nodules (26%), pulmonary fibrosis (23%), lymphadenopathy (13%), pulmonary oedema (13), bronchiectasis (10) and malignancy (9). Other IFs included aortic dissection (1), abdominal aortic aneurysm (5), aortic thrombus (1), pericardial effusion (22), cardiomyaggy (5), lobulated heart lesion (1), obstructed biliary (1) and renal tract (1), pancreatitis (1), incarcerated hiatus hernia (1), free intraperitoneal gas (1) and ruptured breast cyst (1).

Discussion: Proportion of CTPAs positive for PE, 23%, was comparable to other studies. This study further emphasises importance of CTPA in not only diagnosing PE, but also detecting alternate pathologies, thus enabling optimal patient management, though additional costs would have arisen in pursuing the IFs.

Prognostic role of serum gamma-glutamyl transferase levels in patients with pulmonary thromboembolism

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Gamma-glutamyl transferase (GGT) is one of the most important markers of oxidative stress. Serum GGT activity is an independent risk factor for myocardial infarction and cardiac death in patients with coronary artery disease. Serum GGT has not previously been elucidated in the pulmonary thromboembolism (PTE).

The study included 163 patients and spiral chest pulmonary angiography were the most used to confirm acute PE (98%). On admission serum GGT (reference value, 5-61 mg/dL) was measured. Receiver operating characteristic analysis performed to determine the GGT cut-off levels with regard to prognosis. The patients with hepatic disease and alcohol abuse were excluded from the study.

The median age was 72 years, and 106 (65%) were females. All-cause in hospital mortality 14.1% and 30-day mortality was 16.6%. Median GGT levels in patients who died 30-day than in surviving patients was higher (48 mg/dL vs 32 mg/dL, p= 0.3).

Serum GGT values ≤26 mg/dL showed high negative predictive values for all-cause mortality (91%). In univariate analysis, a cut-off level of GGT ≥26 mg/dL for 30-day mortality were OR: 3.1 (95% CI 1.2-7.9).

The present study suggests that serum GGT level appears to be risk stratifica
tion patients with PTE. The results should be confirmed with other randomized prospective studies.

Acute pulmonary embolism in patients of advanced age

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Background: It has been speculated that the atypical clinical presentation of acute pulmonary embolism (PE) in older patients leads to a delay in diagnosis and therefore contributes to the worse prognosis of older patients presenting with acute PE.

Methods: In this single-centre study we investigated the delay in diagnosis and its relation with in-hospital mortality in 202 consecutive patients with acute PE in a period of 14 months. The study population was divided in a younger (<65 years) and an older age group (>65 years).

Results: Older patients present more often hypoxia (p = 0.017) and with a history of syncope (p = 0.046) than younger patients. Delay in diagnosis was not statistically different in both age groups (3.1±3.0 days in the younger and 3.9±3.1 days in the older age group, p=0.450). Age above 65 years was significantly associated with an increased risk for in-hospital mortality (OR 4.36, 95% CI 0.93-20.37, p = 0.043). Delay in diagnosis was not associated with an increase of in-hospital mortality in univariate or multivariate analysis.

Conclusions: The atypical clinical presentation of acute PE in patients older than 65 years cannot be considered as a risk factor for late diagnosis. Moreover, delay in diagnosis is not related to the higher in-hospital death rate of older patients suffering from acute PE.
derwent transhoracic echocardiography, ventilation-perfusion lung scanning and the diagnosis was established with right heart catheterization.

**Results:** Recurrent venous thromboembolism was documented in 8, 7% of patients, with an incidence of 5.9% (95% CI: 0.6-8.4%) and 11.5% after 24 months (95% CI: 5.0-18%). The mortality was 2.6% at 1 year (95% CI: 0.0-5.5%), 3.7% at 2 years (95% CI: 0.0-7.4%) and 7.7% at 5 years (95% CI: 0.0-13.4%). Older age (p=0.046), SPAP>50mmHg and thrombophilia (p=0.005) were significantly associated with increased risk for recurrence. CTPH was developed in 7 of 126 patients (5.6%). During the acute episode of PE, 33 patients (26.2%) presented SPAP<40 mmHg and 54% of them were with SPAP>50mmHg. CTPH developed in 7 of these 33 patients. Severe PH at the time of the acute PE (SPAP>50mmHg) was associated with an increased risk of CTPH (odds ratio: 20.385, SE: 0.88, P<0.005).

**Conclusions:** The rates of recurrent thromboembolism underscore the need for long term follow up. Risk factors must be considered for the duration of anticoagulant therapy. During the first year after an acute episode of PE, CTPH appears to developed in a substantial number of patients. The severity of PH should increase physicians’ awareness for the potential of CTPH.

P2357

**Survey of thrombophilia causes in patient with deep vein thrombosis admitted in Sari’s Imam Khomeini Hospital during 2009**

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**Introduction:** Thrombophilia is a condition in which there is a tendency for clot formation and has an incidence of 1 per 1000 annually. About 2/3 of attacks occurs as DVT and the remainder as PE or associated with DVT. Knowing these hereditary factors can be helpful in designing a proper diagnostic template when after it will be possible for each thrombophilic patient to be diagnosed in its proper way.

**Materials and methods:** This is a descriptive study. Our patients were 70 DVT patients whom were bedridden at Imam hospital, Sari, Mazandran, Iran. After admission, they underwent heparin therapy followed by warfarin therapy for 6 months. In the next stage warfarin was stopped and after 2 weeks of heparin therapy, required lab tests were requested. Needed data were collected by a questionnaire and data were processed by SPSS11 statistical software.

**Findings:** 22 people (31.4%) were males and 48 people (68.6%) were females. Mean age was 42.0(614.6 y. 12 of patients (17.1%) had diminished levels of factor V Leiden while 38 people (52.9%) had normal levels. In 84% of patients there were normal levels of fibrinogen and other 14% had increased levels of fibrinogen.

**Result:**

| V-Leiden | C protein | 2.8% |
| Low fibrinogen | Anti phospholipid | 1.4% |
| Protein S | OCP | 14.5% |
| High-VII | Bedridden | 2.8% |
| High-IX | Pregnancy | 2% |
| III Anti thrombim | Recent surgery | 1.4% |
| G20210A | Malignancy | 1.4% |

**Conclusion:** Our study shows that DVT is most common in females. In through of non lab factors, OCP history of no activity and trauma is more companionship with incidence of DVT. In through of genetic factors, FVL and high level of fibrinogen and low level of 5 protein are common.

P2358

**Pulmonary anatomopathologic analysis and clinical manifestations related to different diseases in patients with pulmonary thromboembolism – An autopsy study**

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Patients, who died due to pulmonary thromboembolism (PTE), may present different clinical manifestations and symptoms depending on their underlying diseases and comorbidities. The aim of this study was describe and associated demographic and etiologic data, anatomic pathological findings and in-vivo manifestations (Acute Respiratory Failure [ARF], Hemodynamic Instability [HI] or Sudden Death) from autopsy reports of PTE patients.

**Methods:** We reviewed 291 autopsies of patients whose cause of death was PTE. The following data were obtained: age, sex, clinical in-vivo manifestations, post-mortem pathological patterns and main associated underlying diseases.

**Results:** The median age was 64 years, 127 men and 164 women. Pulmonary histopathologic changes were: diffuse alveolar damage (DAD), pulmonary edema (PE), alveolar hemorrhage (AH) and lympho-plasmacytic interstitial pneumonia (LIP). The most common clinical manifestation was ARF (28.9%), followed by HI (27.5%) and AH (26.8%). The most prevalent pulmonary finding was PE (26.8%). Chronic Obstructive Pulmonary Disease was positively correlated to LIP (p=0.04). Linking in-vivo manifestations to pulmonary changes were found significative relations between: ARF and PE (OR=2.99; p=0.01); ARF and AH (OR=2.10; p=0.04); ARF and DAD (OR=8.79; p=0.03); HI and HA (OR=3.38, p=0.01) and HI and DAD (OR=1.43; p=0.02).

**Conclusions:** The understanding of pulmonary physiopathological mechanism involved with each PTE-associated disease can improve diagnosis in order to offer prompt treatment and reduce mortality. Financial support: FAPESP, CNPq.

P2359

**Correlation of right ventricular ejection fraction with tricuspid annular plane systolic excursion by electrocardiogram-gated 320 slice CT in chronic thromboembolic pulmonary hypertension**

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**Purpose:** There is a strong correlation between right ventricular ejection fraction (RVEF) and tricuspid annular plane systolic fractional (TAPSE) determined by echocardiography in subjects with pulmonary hypertension (PH). However, it is unknown whether there a correlation between RVEF and TAPSE determined by 320-slice CT. We tested whether TAPSE measured by enhance ECG-gated volume 320-slice CT correlates with RVEF and correlates with pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) obtained by right heart catheterization (RHC) in chronic thromboembolic pulmonary hypertension (CTEPH) subjects.

**Materials and methods:** 33 subjects (11 male, 61±10 yrs) with CTEPH underwent enhanced retrospective ECG-gated volume 320-slice CT (Aquilion ONE, Toshiba) and RHC. CT images were reconstructed every 5% from 0-95% of the R-R interval and a series of apical 4-chamber images. TAPSE was measured from systolic displacement of the RV free wall and tricuspid annular plane junction. RV end-systolic and end-diastolic true volumes were measured from 3-dimensional reconstruction and used to calculate RVEF.

**Results:** TAPSE and RVEF were 14.5±3.5mm and 47.0±14.3%, respectively. In RHC, mean PAP (mPAP) and PVR were 41.4±12 mmHg and 683±364 dyne sec cm⁻⁵, respectively. The correlation coefficient of TAPSE with RVEF was 0.78 (P<0.001). The correlation coefficients of TAPSE with mPAP and PVR were -0.63 (P=0.001) and -0.64 (P<0.001), respectively.

**Conclusions:** TAPSE by ECG-gated 320-slice CT correlated strongly with RVEF and significantly with mPAP and PVR acquired by RHC in subjects with CTEPH.

265. Pulmonary hypertension in hypoxic lung disease

P2360

**Late-breaking abstract: 5-HT mediates susceptibility of rats with low intrinsic aerobic capacity to hypoxia-induced pulmonary hypertension**

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**Introduction:** Low aerobic exercise capacity has been linked with a higher probability of death. We have previously demonstrated that low exercise capacity rats have increased susceptibility to pulmonary arterial hypertension when subjected to chronic hypoxia. Here we investigate the role of 5-HT in conferring susceptibility.

**Methods:** We exposed high and low exercise capacity rats to a 10% O2 environment for 21 days, +/- daily treatment with a 5-HT inhibitor (pCPA). The animals, bred over 21 generations for high (HCR) or low (LCR) running capacity, differed by 500%. PAH biomarkers were determined in heart, lung and blood.

**Results:** LCR rats developed significantly greater PAH pathologies compared to HCR with regard to cardiac and pulmonary vessel remodeling, right ventricular (RV) pressure and echocardiographic measures. Cardiac histology demonstrated pCPA treatment ablated the RV hypertrophic response and myocyte apoptosis in both HCR and LCR animals. 5-HT levels in LCR animals were increased in response to hypoxia, yet unchanged in other groups, and levels in both strains were ablated by pCPA treatment. Although 5-HT effect reduction in all PAH pathologies in all groups, subtractive analysis revealed no impact on the enhanced vessel remodeling and only a partial effect on RV pressure observed in LCR animals. RV mass and echocardiographic measures of RV function, however, were fully reversed.

**Conclusion:** These data support our hypothesis that intrinsically low aerobic capacity may predispose individuals to developing pulmonary arterial hypertension, and that the associated dysregulation of the 5-HT pathway principally impacts RV function rather than vessel remodeling.

425s
**P2361**

**Spirometric corroboration of radiographic changes suggestive of COPD and influence on ventilation-perfusion scanning.**

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**Introduction:** An abnormal chest radiograph (CXR) can affect the ventilation-perfusion (V/Q) scan interpretation in the investigation of suspected pulmonary embolism (PE). V/Q scans are not always preceded by a normal CXR and many CXRs are reported as showing changes “compatible with COPD”.

We decided to ascertain whether radiological suspicion was supported by spirometric evidence of COPD and whether those with more severe COPD were more likely to have an intermediate probability V/Q scan.

**Methods:** All V/Q scans and CXR reports for the 12 months from February 2008 were analysed. The spirometry database was searched and results obtained.

**Results:** 68 patients had V/Q scans with CXRs reported as showing changes compatible with COPD. 44 (65%) had not had spirometry.

Of the 24 (35%) patients with spirometry, 3 reports were unavailable and 19 (90%) were compatible with COPD. The mean FEV1 was 60.2% predicted and the mean FEV1/FVC ratio was 50.7.

The V/Q scan reports are classified according to COPD severity in the table below.

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Number (%)</th>
<th>VQ scan report: Probability of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence COPD</td>
<td>2 (9%)</td>
<td>Low</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (19%)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (24%)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (29%)</td>
<td>High</td>
</tr>
<tr>
<td>Very severe</td>
<td>4 (19%)</td>
<td>High</td>
</tr>
</tbody>
</table>

**Conclusion:** Of the 68 patients reported as having radiological “evidence” of COPD, only 24 (35%) had had spirometry. Of the 21 patients with spirometry reports COPD (91%) did not have COPD.

None of the patients with COPD had an intermediate probability VQ scan. COPD is often “reported” on a chest radiograph but spirometric evidence is not always present and, if present, does not always confirm the radiological suspicion.

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**P2364**

**Non-invasive evaluation in prediction of pulmonary hypertension in patients with idiopathic pulmonary fibrosis.**

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**Introduction:** Pulmonary hypertension (PH) occurs rather frequently in patients with advanced idiopathic pulmonary fibrosis (IPF). However, none of the non-invasive imaging methods is able to predict the utility of drugs for IPF. The aim of this study was to confirm the usefulness of this method in our group of IPF patients.

**Methods:** Pulmonary hypertension (PH) was defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. None of the patients with COPD had an intermediate probability V/Q scan. COPD was often “reported” on a chest radiograph but spirometric evidence is not always present and, if present, does not always confirm the radiological suspicion.

**Results:** Drug therapy with oral vasodilators (both amiodipine or sildenafil) could significantly reduce NT-proBNP levels in COPD-induced PH patients. Also there were no significant differences between amiodipine and sildenafil on lowering NT-proBNP levels (effectiveness of therapies).

**Conclusion:** Drug therapy (oral vasodilators) in COPD-induced significantly decreased NT-proBNP levels in this study. Though, no significant difference between amiodipine and sildenafil in reducing NT-proBNP levels was observed. Changes in NT-proBNP levels could be used as an indicator to monitor the effectiveness of therapies.
The functional abnormalities of right ventricle in long standing chronic obstructive pulmonary disease (COPD) have been well documented. Derangement of the right ventricular (RV) function in these patients, in the absence of other disorders affecting the LV, has not been clearly established.

This study has been designed to provide more definitive information concerning left ventricular function in patients with COPD primarily to ascertain the involvement of left ventricle in stable COPD patients in whom other sources of diastolic dysfunction has been systematically excluded which the previous studies had failed to do.

The aim of the study was to evaluate LV function in COPD patients.

To assess LV function in COPD patients, 30 patients with PH without additional cardiac diseases and 30 age and sex-matched healthy subjects were enrolled into the study.

We defined COPD by GOLD criteria. Well Investigated parameters of Left ventricular diastolic functions like E/A (peak velocity of early E wave /Epeak velocity of early A wave (A transtral flow), IVRT (Isovolumetric relaxation time), MPI (Myocardial Performance Index) were used for the evaluation of LV diastolic function.

The study shows that 30% i.e. 9 of the 30 patients admitted to the hospital with COPD had left ventricular diastolic dysfunction and that the risk of association with Left ventricular diastolic dysfunction is 6 times more in COPD patients than in normal individual.

In COPD patients, LV diastolic function is significantly impaired and its magnitude is related with the severity of COPD as well as the increase in pulmonary artery pressure. This is in spite of preserved LV systolic function.

Drug therapy for pulmonary hypertension associated to chronic lung disease is currently discouraged for the negative effects on gas exchange. We retrospectively studied the effects of long-term treatment with sildenafil is not associated to detrimental effect on gas exchange.

From 2000 to 2007 we identified 14 patients (age 65±7 years) treated with Tadalafil 5 mg (TAD). There was no significant difference in NT-proBNP levels between TAD treated patients and healthy controls (p>0.05). There was a negative correlation between NT-proBNP and PADP (r=0.68). These results mean that ET-1 dysfunction may contribute to increases in pulmonary arterial tone and pulmonary hypertension in COPD.

We conclude: endothelial dysfunction in patients with COPD become intensify from moderate to severe stage, that by-turn influence to increase on central and pulmonary haemodynamics damage. 

**P2366**

The influence of right ventricular diastolic functions and pulmonary hypertension on exercise limitation and their relationship with serum NT-proBNP levels in COPD

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**Introduction:**

During the course of the chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH), right heart failure, exercise limitation develops. Whether pulmonary specific vasodilator treatment with either inhaled Iloprost (Ih), Bosentan (B) or Sildenafil (S) in our PH clinic.

**Methods:**

In this study, 31 moderate-severe COPD patients, 20 healthy controls were included. Right ventricular diastolic parameters, serum NT-proBNP levels were measured. Exercise capacity was evaluated by cardipulmonary exercise testing (CPET).

**Results:**

Echocardiography revealed PH in 13 of the COPD patients. NT-proBNP levels were found to be higher in the COPD group than in the control group, the difference was statistically significant (p<0.05). NT-proBNP level had a relationship with PAP; there was no significant difference in NT-proBNP levels between COPD patients with and without PH (p>0.05). COPD patients demonstrated statisitically lower values than the control group with regard to anechoic threshold oxygen consumption (ATV02) and carbondioxide production (ATVCO2), and peak oxygen consumption (PVO2) and peak carbondioxide production (PVOCO2) (p<0.05). There was a negative correlation between NT-proBNP levels, API, PAP and NT-proBNP values determined by CPET. There was a difference between the COPD and control groups with regard to tricuspid annular plane systolic excursion (TAPSE) value, an echocardiographic parameter (p<0.05).

**Conclusion:**

Demonstration that NT-proBNP levels show a correlation with PH, and they are raised in COPD patients. PH may have a tendency for right ventricular diastolic dysfunction and that exercise limitation might be predicted by right ventricular functions and NT-proBNP levels.
P2371 Pulmonary hypertension and exercise performance in advanced COPD

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Rationale: Pulmonary hypertension is a common occurrence in advanced COPD, but its effects on exercise performance remain unclear.

Aim: To determine the effects of pulmonary hypertension in advanced COPD on exercise performance.

Methods: We conducted the exercise testing and the echocardiographic examination in 32 patients with advanced stable COPD. Mean pulmonary artery pressure (mPAP) was calculated from the acceleration time of pulmonary flow. Exercise capacity was evaluated by the distance walked in 6 min (6MWD) and by an incremental cardiopulmonary exercise test (CPET).

Results: The patients had a forced expiratory volume in 1 s (FEV1) of 1.15±0.34 L (60% predicted, range 22-50%), corresponding to GOLD stages III and IV, and a 6MWD of 310±62 m (mean±SD). The CPET showed: a maximum workload of 50.2±22 W, a peak O2 uptake of 12.4±3.4 mL/kg/min, a peak heart rate of 125±5 bpm, a peak respiratory exchange ratio 1.03±0.7, a ventilation (VE)/CO2 production slope of 34.9±9, and a peak O2 pulse 7.1±1.3 mL/min. The peak VE was 40±13 L/min, and the calculated maximum voluntary VE 42±18 L/min. There was no significant difference in any of the CPET variables and 6MWD between the patients with a mPAP < 30 mm Hg (mPAP 24.4±5 mm Hg, n=17) and those with mPAP > 30 mm Hg (mPAP 33±4 mm Hg, n=15). There was no correlation between PAP and any of the exercise measurements.

Conclusions: These results suggest that exercise performance in patients with advanced COPD and mild to moderate pulmonary hypertension is essentially limited by exhaustion of the ventilatory reserve.

P2372 Presence of established and exercise induced pulmonary hypertension in COPD

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Aim: To describe prevalence of pre-capillary pulmonary hypertension (PH) and exercise induced pulmonary hypertension (EIPH) in COPD without left sided heart diseases, and to relate PH to GOLD stages III-IV.

Methods: 98 patients, 64±7 yrs and 50% men, were recruited. Right heart catheterisation (RHC), performed in 72 (73% of patients), demonstrated pulmonary arterial hypertension (PAH: mPAP > 30mmHg, pulmonary vascular resistance (PVR) > 3 WU) in 22 patients (22.2%). Critical differences between patients with PAH and those without PAH were: higher age, higher exhaled NO and lower exercise capacity. No significant differences were detected in the following variables: FEV1, 6MWD, 6MWT, 6Mmax, VO2 and VO2max (p > 0.05).

Conclusion: PAH is common in COPD with exercise capacity > 6MWD. Exercise induced PAH was not identified in this study. Further studies are needed to evaluate the role of exercise induced pulmonary hypertension in patients with COPD.

P2373 Arterial blood gases during exercise in chronic obstructive pulmonary disease with and without pulmonary hypertension

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Aim: To evaluate blood gas responses during cardiopulmonary exercise test (CPET) when patients with chronic obstructive pulmonary disease (COPD) were categorized by GOLD stages and the presence of pulmonary hypertension (PH).

Methods: Right heart catheterisation (RHC) and CPET to exhaustion with serial blood gas measurements were performed in 98 COPD patients in GOLD stages II-IV without left heart disease. Mean age±SD was 64.7±7 yrs and 50% were men. PH was defined as mean pulmonary artery pressure (mPAP) at rest ≥25mmHg. Results: Table 1. PH was observed in 5, 28 and 51 patients in GOLD stages II, III and IV, respectively. At rest and at peak exercise PaO2 decreased whereas PaCO2 increased with advancing GOLD stages. At rest, only stage IV had lower (p<0.05) PaO2 in patients with PH than in those without. At peak exercise, both stage II and IV had lower (p<0.05) PaO2 in patients with PH than in those without. For PaO2, no significant differences were observed within each GOLD stage.

Table 1

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>n</th>
<th>PaO2 rest, kPa</th>
<th>PaO2 peak, kPa</th>
<th>PaCO2 rest, kPa</th>
<th>PaCO2 peak, kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD II</td>
<td>36</td>
<td>10.2±1.0</td>
<td>9.2±1.0</td>
<td>4±0.9</td>
<td>5±0.9</td>
</tr>
<tr>
<td>GOLD III</td>
<td>21</td>
<td>10.1±1.1</td>
<td>9.1±1.1</td>
<td>4±0.9</td>
<td>5±0.9</td>
</tr>
<tr>
<td>GOLD IV</td>
<td>15</td>
<td>9.2±1.1</td>
<td>8.5±1.0</td>
<td>5±0.9</td>
<td>7.5±1.5</td>
</tr>
</tbody>
</table>

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. PH was a common finding in advanced COPD. Arterial PaO2 at rest and at peak exercise was inversely related to GOLD stages. Presence of PH within each stage was associated with lower PaO2. Since RHC is not available to all COPD patients, CPET is useful in selecting candidates. Low resting PaO2 and excessive decline in PaO2 during exercise justify referral to further PH investigation.

P2374 Experimental hypoxia-induced pulmonary hypertension is prevented by moderate exercise training in mice

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Pulmonary hypertension (PH), a progressive disease of multifactorial etiology, has a poor prognosis and results in right heart dysfunction. PH is characterized by pulmonary vasoconstriction and abnormal vascular remodeling processes. Current medication does not cure the disease; at best disease progression can be mitigated. Main symptoms of PH are fatigue and shortness of breath. Thus, exercise training has been considered as counterproductive in the past. In our study, moderate exercise training prevented pulmonary vascular disease in a mouse model of hypoxia-induced pulmonary hypertension. During 21 days of exposure to hypoxia mice were trained on a treadmill, daily, for five days a week. Readouts were maximum walking distance, maximum oxygen uptake (VO2 max), the effect being similar in trained mice; small vessel muscularization was reduced to a similar degree as with sildenafil-treatment only. Chronic hypoxia induced a significant hypoxia-induced upregulation of PDE5 in whole-tissue treated trained mice; small vessel muscularization was reduced to a similar degree as with sildenafil-treatment only. Chronic hypoxia induced a significant hypoxia-induced upregulation of PDE5 in whole-tissue homogenate, which was absent in trained mice. Overall, our data demonstrate the efficacy of exercise training for prevention of hypoxia-induced pulmonary hypertension, which might be mediated by inhibition of PDE5 upregulation.

P2375 Biomarkers for pulmonary hypertension in interstitial lung disease

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Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (MPAP) ≥ 25 mmHg. New patients with ILD are screened by echocardiography to detect signs of PH. This study evaluates NT-proBNP, D-imeric acid and exhaled NO as biomarkers in diagnosis of PH in patients with ILD. A total of 206 patients with ILD were screened for PH by echocardiography. A tricuspid pressure gradient (TGR) ≥ 40 mmHg, dilatation or decreased tricuspid annular plane systolic excursion (TAPSE) on echocardiography were performed in 98 ILD patients in GOLD stages III-IV with PH. These results suggest that exercise performance both in trained and untrained mice is impaired in PH. Exercise training can prevent and reverse the development of PH, and thus improve exercise capacity in patients with PH.

Results: Mean±SEM: 30 patients had PH based on echocardiography (TGR ≥ 40 mmHg) and positive predictive values (PPV) for detection of PH were calculated.
mmHg). In 19 patients, RHC data were obtained, and in 18, the diagnosis of PH was confirmed (MPAP = 39±2 mmHg). There was a statistical significant relationship between high values of NT-proBNP and the presence of PH, with an area under the ROC curve of 0.85. With a cut-off value of 110 ng/l, higher values of NT-proBNP had a sensitivity of 93%, a specificity of 55%, a PPV = 27% for detecting PH on echo. 47% of the patients had NT-proBNP values below 110 ng/l. There was no statistical significant relationship between the levels of uric acid, fibrin D-dimer and exhaled NO and the presence of PH.

Conclusion: A value of NT-proBNP below 110 ng/l may be used to rule out the presence of PH, and to reduce the need for echocardiographic screening for PH in ILD patients.

266. Treatment of pulmonary hypertension

P2378 Late-breaking abstract: Short term improvement in 6 minute walk distance predicts long term survival in incident idiopathic pulmonary arterial hypertension. Results from the Pulmonary Hypertension Registry of the United Kingdom and Ireland


Background: Improvement in 6 minute walk distance (6MWD) after 12-16 weeks of treatment has been used as the primary end point in many pivotal pulmonary arterial hypertension (PAH) clinical trials. However, the consensus view is that although baseline 6MWD predicts survival, change in 6MWD (Δ6MWD) does not.

Aim: To determine whether Δ6MWD after 3 months of disease targeted therapy predicts long term survival in patients from the Pulmonary Hypertension Registry of the UK and Ireland.

Methods: Retrospective observational study of all incident cases of idiopathic (IPAH), heritable and anorexigen-associated PAH diagnosed in the UK and Ireland between 1st January 2003 and 31st December 2009. Patients were divided into low and high baseline 6MWD by the median 6MWD (295 m).

Results: Total of 646 patients were diagnosed. After 3 months of disease targeted therapy, patients with absolute 6MWD >353 m (corresponding to the median value at 3 months) had better survival than those with 6MWD < 353 m. Mean improvement in 6MWD after 3 months of therapy was 42.4±7.5 m (median 37 m). Patients with greater increase in 6MWD from baseline to 3 months had better post-3 months survival (hazard ratio 0.65, 95% confidence interval 0.42 to 0.99 per 100 metres improvement). In patients with low baseline 6MWD, Δ6MWD at 3 months of > 37.5 m had better survival compared to those with Δ6MWD at 3 months of < 37.5 m (Log-rank, p=0.03). This is not seen in patients with high baseline 6MWD.

Conclusion: Change in 6MWD after 3 months of treatment predicts long term survival in patients with low baseline 6MWD.

P2379 Comparison of hemodynamic effects of inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO) in patients with pulmonary hypertension (PH)

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Background: Acute vasodilator testing with iNO during right heart catheterization in pulmonary arterial hypertension predicts survival and response to calcium channel blockers. iEPO is less expensive than iNO with fewer systemic effects than iNOS and their combination has additive effects.

Methods: Prospective double-blinded study of PH treatment-naïve consecutive patients. Patients >18 years, WHO Group 1-5 with pulmonary capillary wedge pressures < 20 were included. Patients received iNO, iEPO and their combination in random order, with a washout phase between treatments. Hemodynamics at baseline and treatments were reported as±change, means±SD. Correlation was assessed with regression analysis. p<0.05 was significant.

Results: Patients enrolled: Group 1 (11), Group 2 (9), Group 3 (1), Group 4 (1), Group 5 (1). 2 did not complete the study (hypoxemia and dyspnea respectively).

Mean (±SD) iNO 20ppm iEPO 50mcg/kg/min pR2 value

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>iNO 20ppm</th>
<th>iEPO 50mcg/kg/min</th>
<th>R2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%AmPAP</td>
<td>11.9(6.6)</td>
<td>11.5(9.3)</td>
<td>0.57</td>
<td>0.006</td>
</tr>
<tr>
<td>%APVR</td>
<td>18.8(22.9)</td>
<td>16.6(21.7)</td>
<td>0.58</td>
<td>0.006</td>
</tr>
<tr>
<td>%ACO</td>
<td>4.1(2.5)</td>
<td>7.5(1.9)</td>
<td>0.52</td>
<td>0.01</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%AmPAP</td>
<td>6.0(9.6)</td>
<td>8.4(11.1)</td>
<td>0.59</td>
<td>0.014</td>
</tr>
<tr>
<td>%APVR</td>
<td>25.8(24.6)</td>
<td>25.2(27.2)</td>
<td>0.55</td>
<td>0.021</td>
</tr>
<tr>
<td>%ACO</td>
<td>12.2(26.5)</td>
<td>6.4(18.2)</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

R2: is the correction factor for the variability in the adjusting factors. %AmPAP, %APVR, %ACO were mean pulmonary vascular resistances (PVR) at 2 AT and 30 AT respectively.
A statistically significant reduction (p=0.006) in PVR was observed. There
was a 10-minute interval. Pulmonary and systemic haemodynamic measurements were recorded at
mean PAP was 75 \pm 13 mmHg, cardiac index 2.0 \pm 0.6 L/min/m^2 and pulmonary vascular resistance 1194 \pm 571 dyn cm^-5. In the overall PH population, survival estimates following epo commencement were 77%, 63% and 54% at 1, 2 and 3 years, respectively, and 82%, 72% and 69% in the subgroup of pts with PAH.

Conclusion: Epo is still used as first-line therapy in severe forms of PH. It is
notably prescribed in non-group 1 PH in 28% of cases. In incident pts with PAH, 1- and 2-year survival is similar to historical cohorts, despite the prior use of an oral treatment in 48% of them.

Methods: 30 SLE patients with PAH (mean age is 48.3±1.7 yrs) were studied, whom to conventional therapy was added “Korargin” 2 tablets 3 times a day for 8 weeks. The object of the effectiveness was increased distance of 6-minute walk (6MW), changes in pulmonary artery pressure and improvement of functional class (FC) PAH on WHO.

Results: II FC PAH was diagnosed in 80% patients. Patients with III FC was 20%.
From the 4th week and untill the end of the initial study, the patients demonstrated a significant increase in the distance test of 6MW an average of 61.2±3.2 m compared with the baseline data. In addition, it was observed decrease in pulmonary arterial pressure on 11% in 37% of patients, 64% patients improved their FC.

Conclusion: Despite of the fact, that insufficient long-term follow-up period and relatively non-severe population of SLE patients with PAH, having taken “Korargin”, patients has improved tolerance to physical activity, FC PAH on WHO and hemodynamic parameters.

P2384

Impact of functional class change on survival in patients with pulmonary arterial hypertension in the REVEAL registry
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Introduction: The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), a 55-center observational, US-based study, describes current demographic, clinical, and treatment patterns in PAH patients (pts).

Objective: Determine if pts who improve from functional class (FC) III at enroll ment to FC III if follow-up (fu) have a better 2-year survival than pts who remain FC III.

Methods: 1,082 adults enrolled in REVEAL were assessed as FC III at enrollment (based on most recent pre-enrollment evaluation) and had ≥ 1 fu FC assessment within the first year after enrollment. We classified pts based on their first fu assessment after enrollment as: 1) improved if FC improved to FC II; 2) unchanged if remained FC III; or 3) deteriorated if worsened to FC IV. We compared survival (estimates±SE) of these 3 subgroups from the first fu FC assessment (log-rank test).

Results: FC improved in 26% (n=281) of pts, was unchanged in 66% (n=718) and deteriorated in 8% (n=83). At enrollment, there were no differences in gender, PAH subgroup, right atrial pressure, or cardiac index; significant differences were observed in age, proportion of newly diagnosed (diagnostic confirmatory cardiac catheterization <3 months before enrollment) pts, and 6-minute walk distance among groups. Two-year survival was 88.2%, 76.2%, and 34.6% for FC III, FC I/II, and FC IV pts, respectively (P<0.001 for all pairwise comparisons). Results are similar for both newly and previously diagnosed pts who were FC III at enrollment.

Conclusions: Pts who improve from FC III to FC I/II appear to have a better

P2385

Effectiveness of “Korargin” in the therapy of pulmonary arterial hypertension in patients with systemic lupus erythematosus
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Introduction: Pulmonary arterial hypertension (PAH) in systemic lupus erythematosus (SLE) is a complex therapeutic problem and occurs from 5 to 14%. The main pathophysiological mechanism of PAH is an endothelium dysfunction with abnormality of nitric oxide synthesis (Ghorbani H.A. et al. J. Am. Coll. Cardiol. 2004; 43: 688-72S).

Objective was to examine the efficacy of the “Korargin” (1 tablet contains 0.1g L-arginine and 0.1g isosorbide), production of “Korargin”, Uman, Ukraine in SLE patients with PAH.

Methods: 30 SLE patients with PAH (mean age is 48.3±1.7 yrs) were studied, whom to conventional therapy was added “Korargin” 2 tablets 3 times a day for 8 weeks. The object of the effectiveness was increased distance of 6-minute walk (6MW), changes in pulmonary artery pressure and improvement of functional class (FC) PAH on WHO.

Results: II FC PAH was diagnosed in 80% patients. Patients with III FC was 20%.
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Conclusion: Despite of the fact, that insufficient long-term follow-up period and relatively non-severe population of SLE patients with PAH, having taken “Korargin”, patients has improved tolerance to physical activity, FC PAH on WHO and hemodynamic parameters.

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Conclusions: Pts who improve from FC III to FC I/II appear to have a better
**P2385**

**Inhaled treprostinil therapy in patients with pulmonary hypertension and parenchymal lung disease**

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The treatment of patients with Parenchymal Lung Disease (PLD) and Pulmonary Hypertension (PH) is challenging. PLD is characterized by an imbalance between alveolar ventilation and pulmonary blood flow. The ability to deliver therapy to areas of lung that are well ventilated would utilize preserved V/Q matching and improve drug delivery. This would reduce undesirable alterations in perfusion caused by a systemic vasodilator and provide a more effective way of treating these patients. We examined the response of patients with PLD and PH receiving Inhaled Treprostinil. We followed eight patients with NYHA Functional Class III/IV symptoms with a mean PAP >25mmHg and PCWP of ≥15mmHg for at least 3 months. Five subjects had Obstructive Lung Disease and three were classified as having Restrictive Lung Disease. All followed the usual protocol starting with three breaths four times a day and gradually increased to the goal of nine breaths a day.

Two patients had to be reduced to six breaths a day due to threat of irritation but were able to increase back to nine breaths a day. One patient stopped the Inhaled Treprostinil one week after starting therapy for worsening symptoms of shortness of breath. Two patients were on a background PDE5 Inhibitor prior to starting the inhaled treatment. All but one patient reported less shortness of breath after initiation of treatment. The majority of patients had an improvement in 6-MWD and Borg Dyspnea Scale. Our experience suggests that patients with PLD and PH can be safely treated with inhaled Treprostinil. Inhaled Treprostinil may offer an effective and well tolerated treatment in subjects with PLD and shortness of breath exacerbated by PH.

**P2386**

**Parenteral treprostinil for significant pulmonary arterial hypertension associated with pulmonary fibrosis: A safety study**

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Objectives: Safety & efficacy of treprostinil (IV/SQ) in patients with pulmonary fibrosis (PF) and PAH.

Methods: Prospective, open label trial of patients referred for lung transplantation with PPH/PAH (mean PA >35 mmHg & PVR >3 WU), treated treprostinil × 12 weeks.

Results: N=14 received treprostinil (18-97 mg/kg/min). The hemodynamics, 6MW, BNP, and UCSD/SF 36 significantly improved. No significant changes were seen with PF/PAH. Prospective, multicenter, randomized-controlled studies are warranted to verify these results.

**Conclusions:** Chronic administration of treprostinil is well tolerated in patients with PPH/PAH. Prospective, multicenter, randomized-controlled studies are warranted to verify these results.

**P2387**

Cardiotoxic agents affect pulmonary vessels in precision-cut lung slices (PCLS)

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1Institute of Pharmacology and Toxicology, Medical Faculty of RWTH Aachen, Aachen, Germany; 2Department of Anaesthesiology, Medical Faculty of RWTH Aachen, Aachen, Germany

Introduction: Cardiotoxic agents play a major role in the therapy of heart failure. Apart from their effects on ventricular contractility and systemic afterload, they may affect the tone of pulmonary arteries (PAs) and pulmonary veins (PVs). However, in particular the responses of PVs to cardiotoxic agents are only poorly defined.

Aims and objectives: We investigated the effects of α- and β-adrenergic agents as well as vasopressin in PAs and PVs to clarify their potential role in pulmonary hypertension (PH) or lung edema and coexisting heart failure.

Methods: After terminal anaesthesia with pentobarbital, PCLS were prepared from female Dunken Hartley guinea pigs and investigated by video microscopy. Concentration-response curves of various cardiotoxic drugs were analyzed in PAs and PVs.

Results: After stimulation with α1-adrenergic agents, PAs contracted up to 80.5% ± 3, in respect to the initial vessel area, whereas β2-adrenergic agents showed only little effect. In contrast, after stimulation of β2-receptors PVs contracted up to 77% ± 2.6 and relaxed due to activation of β2-receptors up to 124.7% ± 2.8. Notably, inhibition of β2-receptors unmasked the α1-mimetic effect of (nor)epinephrine. Vasopressin contracted PAs up to 76.4% ± 4.24, without any effect on PVs.

Conclusion: Thus, vasodilatation of PAs enhances capillary and venous hydrostatic pressures and promotes the development of lung edema. Our findings suggest that (nor)epinephrine in combination with unselective β-blockers and vasopressin might be harmful in patients with left heart failure. Further, α1-mimetic agents might exacerbate a pre-existing PH and a failing right ventricle by contracting PAs, whereas vasopressin might not.

**P2388**

Stability and microbial properties of reconstituted and diluted epoprostenol with expanded stability with expanded stability

Oliver Lambert1, Dirk Bandilla2, Rupa Iyer1, Leonore Whyte-Lakshmanan1, Nagesh Palepu3. 1Drug Product Operations, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 2Global Quality Management, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 3President, TPM Laboratories, Inc., Cherry Hill, NJ, United States; 4Principal Consultant, Pharma CMC and IP, Piscataway, NJ, United States; 5President and CSO, SciDose LLC, Amherst, MA, United States

Microbial activity and stability of epoprostenol with expanded stability (EPO-ES, Veletri®) were investigated at 5°C and 25°C over a range of concentrations. EPO-ES was reconstituted and immediately diluted with sterile Water for Injection (WFI) or Sodium Chloride 0.9% Injection (NaCl). Stability for up to 72 hours (B) at 25°C was measured immediately following dilution (A), and after 1 (B) or 7 days (C) storage at 5°C. Shelf-life was assessed by determining the time over which potency ≥90% was maintained. For microbiological testing, diluted samples of EPO-ES were inoculated with S. aureus, P. aeruginosa, E. coli, C. albicans, A. niger or C. sporogenes and incubated for up to 14 days at 35°C or 4 days at 25°C. Potency of EPO-ES 6,000 ng/mL at 12h under test condition B was 92% for both diluents. Potency of EPO-ES 9,000 ng/mL under test condition C was 91% for WFI and 87% for NaCl at 12h, and ≥90% for both diluents at 12 and 24 h at 12,000

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Age (year) (SD)</th>
<th>NPYHA Class (n=14)</th>
<th>IV</th>
<th>Hispanic</th>
<th>Caucasian</th>
<th>Middle Eastern</th>
<th>Caucasian</th>
<th>Filipino</th>
<th>Diffuse Lung Disease</th>
<th>Idiopathic Pulmonary Fibrosis (IPF)</th>
<th>NSF fibrosis</th>
<th>Chronic Hypersensitivity Pneumonitis</th>
<th>Pulmonary Fibrosis, unknown</th>
<th>EPO-ES (ng/mL)</th>
<th>Potency of EPO-ES 6,000 ng/mL at 12h under test condition B</th>
<th>Potency of EPO-ES 9,000 ng/mL under test condition C</th>
</tr>
</thead>
</table>
| 63 (14)        | III               | 7/14 (50%) | 7/14 (50%) | 8/14 (57%) | 4/14 (29%)    | 1/14 (7%) | 1/14 (7%) | IPF/Emphysema (CPFE) | 4/14 (29%)                  | 4/14 (29%) | 4/14 (29%)                     | 1/7 (14%)                  | 3/7 (43%) | Potency of EPO-ES 6,000 ng/mL at 12h under test condition B was 92% for both diluents | Potency of EPO-ES 9,000 ng/mL under test condition C was 91% for WFI and 87% for NaCl at 12h, and ≥90% for both diluents at 12 and 24 h at 12,000

Conclusions: Chronic administration of treprostinil is well tolerated in patients with PPH/PAH. Prospective, multicenter, randomized-controlled studies are warranted to verify these results.

**P2388**

Stability and microbial properties of reconstituted and diluted epoprostenol with expanded stability

Oliver Lambert1, Dirk Bandilla2, Rupa Iyer1, Leonore Whyte-Lakshmanan1, Nagesh Palepu3. 1Drug Product Operations, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 2Global Quality Management, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 3President, TPM Laboratories, Inc., Cherry Hill, NJ, United States; 4Principal Consultant, Pharma CMC and IP, Piscataway, NJ, United States; 5President and CSO, SciDose LLC, Amherst, MA, United States

Microbial activity and stability of epoprostenol with expanded stability (EPO-ES, Veletri®) were investigated at 5°C and 25°C over a range of concentrations. EPO-ES was reconstituted and immediately diluted with sterile Water for Injection (WFI) or Sodium Chloride 0.9% Injection (NaCl). Stability for up to 72 hours (B) at 25°C was measured immediately following dilution (A), and after 1 (B) or 7 days (C) storage at 5°C. Shelf-life was assessed by determining the time over which potency ≥90% was maintained. For microbiological testing, diluted samples of EPO-ES were inoculated with S. aureus, P. aeruginosa, E. coli, C. albicans, A. niger or C. sporogenes and incubated for up to 14 days at 35°C or 4 days at 25°C. Potency of EPO-ES 6,000 ng/mL at 12h under test condition B was 92% for both diluents. Potency of EPO-ES 9,000 ng/mL under test condition C was 91% for WFI and 87% for NaCl at 12h, and ≥90% for both diluents at 12 and 24 h at 12,000
Introduction: Careful and frequent assessment is important for management of patient with pulmonary hypertension (PH). Cardiac output (CO) is one of the most relevant indexes to be assessed but cannot be performed routinely because of invasive determination. A simple non-invasive method, such as nitrous oxide inert gas rebreathing (REB) could be performed at every clinic visit.

Aims and objective: To evaluate the possibility to follow up CO by REB against thermodilution (TD) in patients with severe PH. (Dana Point class 1 and 4)

Method: CO and Stroke volume (SV) were determined via TD and REB at two different visits and spearman correlation were applied.

Results: Good correlations were found between TD and REB Δ (visit 1 – visit 2) CO and ΔSV. TD and REB ΔCO and ΔSV correlated similarly with other indexes of clinical assessment.

Table 2. Shelf-life (hours) of reconstituted and immediately diluted EPO-ES at 25°C based on potency and microbiological testing

<table>
<thead>
<tr>
<th>EpoProstol/ES, ng/mL</th>
<th>Condition A</th>
<th>Condition B</th>
<th>Condition C</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3,000 – &lt;6,000</td>
<td>12</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>≥6,000 – &lt;9,000</td>
<td>24</td>
<td>12</td>
<td>Do not use</td>
</tr>
<tr>
<td>≥9,000 – &lt;12,000</td>
<td>24</td>
<td>12</td>
<td>12</td>
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<tr>
<td>≥12,000 – &lt;30,000</td>
<td>24</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>≥30,000</td>
<td>72</td>
<td>48</td>
<td>24</td>
</tr>
</tbody>
</table>

P2389

Cardiac output measured by rebreathing nitrous oxide for the follow-up of patient with pulmonary hypertension

Gael Debeck, Robert McKenzie Ross, Joanna Pepe-Zaba. PVDU, Papworth Hospital, Papworth, United Kingdom

Introduction: Careful and frequent assessment is important for management of

and 30,000 ng/mL. No microbial proliferation occurred in any diluted solution of EPO-ES.

P2390

Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States

Use of non invasive gas exchange to track pulmonary vascular responses to exercise in heart failure

Paul Woods, Bryan Taylor, Thomas Olson, Bruce Johnson. Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States

Simple metrics to quantify severity of pulmonary hypertension (PH) are lacking, particularly with exercise. Studies have suggested that end tidal CO₂ (PetCO₂) and ventilatory efficiency (Ve/VCO₂) may be good indicators of the pulmonary vascular (PV) response to exercise in patients with PH. In addition, measures of PV capacitance (stroke volume/pulmonary arterial pressure, Pvcap) are predictive of survival in the PH population and may potentially be estimated with gas exchange. PH is common in heart failure (HF) and appears to have both passive and reactive components. However, HF is associated with a number of gas exchange abnormalities that could limit the ability of using PetCO₂ or Ve/VCO₂ to estimate the presence of PH. The focus of this study was, a) determine how well non-invasive gas exchange tracks the PV response to exercise and b) test a non-invasive estimate of Pvcap. Forty-two patients with HF (age 54±9, LVEF 20±6, NYHA class 3±1) undergoing r.-hrt catheterization as part of a pre-transplant evaluation were studied. PV pressures (Ppa/Ppw), cardiac output and PV resistance (PVR) were obtained with simultaneous measures of gas exchange. PetCO₂ and Ve/VCO₂ obtained during moderate exercise (VO₂ 9±2ml/kg/min, 37±13W) were highly correlated (r =0.95) and thus data were analyzed in tertiles according to PetCO₂ (mean 23±3, 29±2, 36±4mmHg). PVR followed a decreasing trend from low to high PetCO₂ groups (365±256, 282±162, 188±41WU, p<0.01, r=0.47). Pvcap from catheter measures was highly associated with a value estimated from Qp/Qs (Intercept/1/PetCO₂) (r=0.84). Non invasive gas exchange measures may represent a relatively simple way to track PV response to exercise in HF: NIH HL71478.

P2391

Use of non invasive gas exchange to track pulmonary vascular responses to exercise in heart failure

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Simple metrics to quantify severity of pulmonary hypertension (PH) are lacking, particularly with exercise. Studies have suggested that end tidal CO₂ (PetCO₂) and ventilatory efficiency (Ve/VCO₂) may be good indicators of the pulmonary vascular (PV) response to exercise in patients with PH. In addition, measures of PV capacitance (stroke volume/pulmonary arterial pressure, Pvcap) are predictive of survival in the PH population and may potentially be estimated with gas exchange. PH is common in heart failure (HF) and appears to have both passive and reactive components. However, HF is associated with a number of gas exchange abnormalities that could limit the ability of using PetCO₂ or Ve/VCO₂ to estimate the presence of PH. The focus of this study was, a) determine how well non-invasive gas exchange tracks the PV response to exercise and b) test a non-invasive estimate of Pvcap. Forty-two patients with HF (age 54±9, LVEF 20±6, NYHA class 3±1) undergoing r.-hrt catheterization as part of a pre-transplant evaluation were studied. PV pressures (Ppa/Ppw), cardiac output and PV resistance (PVR) were obtained with simultaneous measures of gas exchange. PetCO₂ and Ve/VCO₂ obtained during moderate exercise (VO₂ 9±2ml/kg/min, 37±13W) were highly correlated (r =0.95) and thus data were analyzed in tertiles according to PetCO₂ (mean 23±3, 29±2, 36±4mmHg). PVR followed a decreasing trend from low to high PetCO₂ groups (365±256, 282±162, 188±41WU, p<0.01, r=0.47). Pvcap from catheter measures was highly associated with a value estimated from Qp/Qs (Intercept/1/PetCO₂) (r=0.84). Non invasive gas exchange measures may represent a relatively simple way to track PV response to exercise in HF: NIH HL71478.

P2392

Is flying safe for individuals with pulmonary arteriovenous malformations and hereditary haemorrhagic telangiectasia? A questionnaire-based study

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Background: Flight-related complications reported in individuals with pulmonary arteriovenous malformations (PVMs) and hereditary haemorrhagic telangiectasia (HHT) have included deep venous thrombosis (DVT), ischaemic stroke, and haemorrhage from PVMs. In addition there are concerns that the reduced barometric pressure associated with flying might exacerbate PVM-induced hypoxia.

Methods: With ethical approval (NRES 10/H010/006), individuals with PVMs and/or HHT were sent a questionnaire to document flights they had taken, and symptoms experienced during or shortly afterwards. Responses were correlated with sea level erect oxygen saturations (SaO₂), and haemoglobin (Hb).

Results: 159 replies were received (response rate 52%). 147 individuals had flown, 97 (66%) with PVMs. The median number of flights per individual was 25, totalling 18,943 flight hours in 3,950 flights. 111 (77%) respondents reported no complications. Six (4%) reported dyspnoea, two (1%) had a deep vein thrombosis, and one had an ischaemic stroke whilst flying. However the most common in-flight complications were HHT-related nosebleeds, reported by 26 (18%). There was no difference in SaO₂ at sea level between those who reported dyspnoea, and those who did not (medians 93 [range 85–96%]; 94 [84–99%]). There was

Table 1. Potency of EPO-ES over time (Condition A)

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<th>EPO-ES, ng/mL</th>
<th>Diluent</th>
<th>Potency, %</th>
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WITHDRAWN
also no difference in Hb measured in clinic between the groups that developed complications, and those who did not.

Conclusion: Flight appears safe for the majority of individuals with PAVMs and JHHT. It is difficult to predict who will experience complications. Recognition of potential thrombotic and haemorrhagic sequelae should influence pre-flight advice.

P2393

Is there an association between hyperthyroidism and PAH and, if yes, is pulmonary pressure decreasing after hyperthyroid treatment?

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Rationale: About 30-40% of patients of idiopathic pulmonary arterial hypertension (IPAH) have thyroid dysfunction, in particular hyperthyroidism. Pulmonary vascular remodeling in IPAH is characterized by proliferation of vascular cells and thyroid hormones are known to promote angiogenesis (Mousa et al J Cardiovasc Pharmacol, 2005). We therefore hypothesized that hyperthyroidism would improve pulmonary vascular remodeling in a model of angio proliferative pulmonary hypertension (SuHx model).

Objectives: To clarify the effect of thyroid hormone on pulmonary vascular remodeling in SuHx treated rats.

Methods: PaH was induced by the combined exposure of rats to the VEGF receptor blocker SU5416 and hypoxia (SuHx). Hypothyroidism was induced by PTU (10mg/kg, 3times a week), two weeks after the initial SU5416 dose (SuHx rats). RF function was determined by echocardiography. Right ventricular pressure was measured by direct insertion of a conductance catheter into the heart.

Results: In SuHx rats, pulmonary vascular remodeling and pulmonary hypertension were decreased after PTU treatment and completely suppressed after thyroideectomy.

Conclusions: Thyroid dysfunction may affect the progression of pulmonary vascular cell proliferation in patients with PAH.

P2394

Immunosuppression in systemic lupus erythematosus associated pulmonary arterial hypertension (SLE-PAH): Improvement in exercise and functional capacity

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Evidence suggests that inflammation plays a role in the pathogenesis of SLE-PAH. We aimed to assess the effect of aggressive immunosuppression (IMM) added to PAH-specific therapy in SLE-PAH. Stanford’s PAH database was searched for patients who met American College of Rheumatology (ACR) criteria for SLE and had PAH by right heart catheterization. Those who met ACR criteria for other connective tissue diseases or had <6 months of follow-up were excluded. Patients given IMM compared to those on PAH-specific therapy only (non-IMM). Cumulative probability of freedom from worsening New York Heart Association functional class (FC) was calculated with the Kaplan-Meier estimator and compared by the log rank test. Mean changes in parameters between groups were compared by Student’s t-test. Thirteen patients met inclusion criteria; 6 were treated with IMM (3 high dose steroids+mycophenolate mofetil, 2 intravenous cyclophosphamide, 1 hematopoietic stem cell transplant). Mean follow-up was 12.9 months. There was no significant difference in baseline demographics, SLE features, duration of PAH, hemodynamics, FC, 6 minute walk distance (6MWD) or PAH-specific therapy between IMM and non-IMM groups. At follow-up, hemodynamics and PAH-specific therapy did not differ between groups. Mean improvements in FC (-1.2 vs 0.1, p=0.06) and 6MWD (+231 vs -20, p=0.02) were higher in the IMM group. The IMM group had more infections (1.8 vs 0.3, p=0.05), but the percent of patients with serious infections did not differ (33% vs 14%, p=0.56). IMM added to PAH-specific therapy may improve functional and exercise capacity in SLE-PAH.

P2395

Monitoring of liver function in patients with pulmonary hypertension treated with endothelin receptor antagonists: The value of a novel monitoring system

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Background: Endothelin receptor antagonists are used for treatment of pulmonary arterial hypertension (PAH). However, these drugs have been associated with liver injury and patients require regular monitoring of liver function (LFT). We introduced a postal system whereby patients receiving these therapies had blood taken by their local practitioner and sent pre packaged boxes to our centre for analysis and monitoring on a monthly basis.

Objective: To evaluate the efficacy of surgery in the blunt traumatic diaphragmatic lesions.

Material and methods: From 1990 to 2010 a total of 24 patients (pts) (3 female and 21 male, mean age 47.1y) were operated on. Time from trauma to surgery varied between 4 months to 8 years. The left hemidiaphragm was injured in 17 cases, while the right one in 7. The thoracic trauma was associated with other injuries in 10 pts. In 3pts incarceration of herniated visceral segment was observed. In 2 pts herniated stomach had been drained for “pneumothorax” and emergency surgery was carried out.

Results: Laparotomy was applied in 3 pts with stomach volvulus. In 21 cases thoracotomy was the surgical approach. Stomach, colon, small bowel, omentum and spleen were most frequently found to herniated through the left diaphragmatic defects, whereas colon and liver were mostly seen in the right enterothorax. In 1 patient transdiaphragmatic splenectomy was carried out because of a severe induration. Dense adhesions were found in all cases. Mayo technique was performed in 19 pts for diaphragmatic repair. Marlex mesh was used in 4 pts and in 1 case an original technique for repair of enormous diaphragmatic defect with pericardial flap was carried out. Uneventful postoperative period was observed in all but one patient.
Objectives: Spirometry was assessed in patients before and after full-length phrenic nerve transfer surgery.

Methods: 16 patients (13 men; 7 to 58 years old) with brachial plexus injury underwent full-length phrenic nerve transfer. By video-assisted thoracic surgery the phrenic nerve was severed at a location just before its entry into the diaphragm, harvested from the thoracic cavity, and transferred to the musculocutaneous nerve. The median time between injury and surgery was 5.5 months (range 2.8 to 10.2). Patients underwent follow-up evaluation 1.4 to 16.4 months with manual muscle testing and spirometry; 3 patients were eventually lost to follow up.

Results: Baseline spirometric parameters were normal. Although no patient experienced pulmonary problems or respiratory complaints following the surgery, we observed a significant reduction of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC, respectively, to 68% of predicted values (±17; p<0.001) and 81% (±17; p=0.03). The percent variation of FVC was -22% (±11; range -49% to -6%). We observed a negative dependence between FVC and length of time after surgery (Figure: The majority of patients exhibit motor improvement on the arm.

Conclusion: Although preliminary, our results point to a significant impact of the surgery to spirometric parameters. This impact improves with the time after surgery.

P2400

Omentoplasty in rabbit for the repair of diaphragmatic defect and adhesion assessment of viscera to propylene mesh.

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Background: The use of synthetic mesh for the repair of major congenital diaphragmatic hernia may cause visceral adhesion to prosthesis and ongoing complications. In present study the use of propylene mesh for the repair of diaphragmatic hernia and its role in eliminating of visceral adhesion to repair site is evaluated.

Materials & methods: This experimental study was carried out on 20 adult New Zealand rabbits (age: 6 months) assigned randomly into two equal groups. In one group, after laparotomy a defect (size: 1×1 cm) was created on the diaphragm. The suture was then repaired by sterile propylene mesh and nylon suture (thickness: 3/0; 4/0). In another group, omentum was fixed on the mesh using a nylon suture (thickness: 3/0). After 30 days the two groups were operated and the visceral adhesion to repair site was compared using Muzafi scale.

Results: Nine (90%) out of 10 rabbits with propylene mesh repair had visceral adhesion to the repair site. On classifying the grade of adhesion among the cases, one, three, four and two rabbits were assigned the “I”, “II”, “III”, and “IV” grades, respectively. On the other hand, 4 (40%) out of 10 rabbits, in which the diaphragm was repaired by propylene mesh and omentoplasty method, visceral adhesion (grade “I”) was seen to the site of repair. The rest of animals displayed no such adhesion (P=0.015).

Conclusions: Omentoplasty after repair of large diaphragmatic defect with propylene mesh reduces the visceral adhesion to propylene mesh, so in intraabdominal operations which propylene mesh is used, omentoplasty also is recommended.
There were 32 consecutive patients in a single city state hospital in Turkey. Median age of the patients was 42.4 (22 min 78 max). There were 27 male and 5 female patients. Admission to the ER were due to blunt trauma caused by falling down or motor vehicle accident. The patients who needed to have chest tube insertion either due to pneumothorax or hemorarx were excluded from the study. The Visual Analog Pain Scale was asked every patient before starting treatment. Mean value was 7.8 were patients with fractured ribs (n=12) and 7.3 for the patients without fracture in the ribs (n=20). After the intercostal blockage and the analgesic treatment themean values decreased to 4.2 and 4 respectively in the following 24 hour. The patients discharged from the hospital in the following 3-4 days. The injection of bupivacaine 5% was to 1ml to 3 levels. First was to the site having the most severe pain to the palpation plus one level up and down with the well known standardized method. The procedure was repeated every day during the hospitalization period.

Application of 5% bupivacaine into the intercostal space to patients having pain is safe and effective. It decreases the Visual Analogue Pain Scale rapidly, need for non opioid analgesics and decreases the hospitalization period and possible morbidities due to secretion retention. It evidently improves the patients comfort.

**P2403**

**Effectiveness of treatment of transdermal narcotics in rib fractures**

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Ribs fracture is the most common pathology in thoracic traumas. Severe pain is the most common symptom. The use and dosage of narcotic analgesics in the early period is controversial. Our aim is to investigate the efficacy of transdermal release (TR) narcotics in these patients. There were consecutive 25 patients who had diagnosis of rib fractures. Patients in group 1 (n=10) had intercostal nerve block (by bupivacain 0.5%), intramuscular narcotic (meperidine) according to the weight of the patient and paracetamol per orally. Patients in group 2 (n=15) intercostal nerve block (by bupivacain 0.5%), transdermal release (TR) narcotics (fentanyl) and paracetamol orally. We used Visual Analog Scale (VAS) for scoring the pain. The efficacy of treatment is evaluated by calculation and scoring of VOAS both at exertion and relaxation. The sedation that might be by the narcotic agents was followed by Ramsey Sedation Scale (RSS) and arterial blood gases. The study was ended in the fifty day. There were no difference for age, gender, type of trauma, additional pathologies number of fractured ribs and their localization between the two groups. Both groups had improvement for VAS before and after treatment. The VAS improvement in group 2 was better in both in relaxation and activity for the 5 days.

It is difficult to establish the effective blood levels of parenteral narcotics so that there is continuous need for repetitive administration of the drugs. In TD applied narcotics the blood levels of the drugs are stable. The use of narcotics transdermally instead of parenteral administration was more effective and comfortable by the way of administration according to our study results.

**P2404**

**Chest wall stabilization with titanium clips and rib bridge: Four case reports**

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Introduction: Chest wall stabilization has a paramount importance. Herein, we aimed to present our experience with the using titanium clips and rib bridges in the chest wall stabilization.

Case 1: A 50-year-old man was referred to our clinic with multiple rib fractures on the left side, bilateral lung contusion, left sided pneumothorax and left clavicular fracture. A chest tube has been inserted to the left side and he has been extubated because of respiratory insufficiency. He was extubated successfully. Although the lung contusion resolved, his blood saturation decreased frequently due to flail chest and secretion retention. We performed 5th,6th and 7th ribs stabilization with titanium rib clip with 9 segments.

Case 2: A 73-year-old man admitted with chest pain and dyspnea. He had a motor vehicle accident two months ago and he had treatment for multiple rib fractures (4,5,6 and 7 ribs) and hemorarx on the right side. He underwent 4th and 5th ribs stabilization with titanium rib clip with 4 and 5 segments.

Case 3: A 21-year old male admitted with the unstable anterior chest wall. He was operated two times for deformity. His clinical presentation was compatible with floating sternum as a long-term complication. He underwent sternum stabilization with two implant bridges. He was discharged on the 5th postoperative day.

Case 4: A 58-year old male admitted with right upper lobe tumor which was invasive to the anterior chest wall. He underwent right upper lobectomy with chest wall resection including 2,3 and 4 ribs. We placed an implant bridge on the 3th rib.

Conclusion: Rigid materials such as titanium clips and titanium rib bridge are good alternative choice for the stabilization of chest wall.

**P2405**

**Intercostal nerve blockage for pain control in blunt thoracic trauma**

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Blunt thoracic traumas are common clinical occasions in the emergency rooms. There are several approaches in the medical management of these patients. In this study we evaluated the the safety and efficacy of application of long acting local anesthetic bupivacaine 5% in to the intercostal space.

Surgery: The surgical approach was very simply with incision and drainage.

Postoperative outcomes: The evolution was very good with discharge of the patient 7 days after.

Discussion: The principal diferential diagnosis was the cold abscess, but all analyses were negative and the evolution was favorable without specified treatment.
Minimally invasive repair for pectus excavatum (Nuss procedure) – Aesthetic and/or functional? 
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Background: Pectus excavatum is the most frequent anterior thoracic wall congenital malformation. Among teenagers, when the esthetics and clinical symptoms become increasingly important, pectus excavatum becomes a psychological problem. During the time many treatment techniques have been proposed, conservative or surgical. The minimally invasive repair technique of pectus excavatum, Nuss technique, developed after 1986, is now the most used technique worldwide. 

Objectives: Our study aimed to analyze the degree of patients satisfaction regarding the esthetic results after the minimally invasive repair of pectus excavatum, as well as the improvement of respiratory functional parameters.

Method: We will present some historical data related to surgical repair of pectus excavatum, advantages and disadvantages of open surgery; also we will present clinical and paraclinical evaluations, including anthropometric indexes, as well as indications and contraindications of Nuss technique and possible intraoperative and postoperative complications.

Our study was carried out on a group of patients with pectus excavatum, who have been submitted to Nuss technique, during a timeframe of 4 years (2007 – 2011), aged from 8 to 38 years. Prior to surgery the patients were submitted to a standard protocol of investigations.

Results: We present the benefits of Nuss technique and the improvements of the functional and aesthetical indexes.

Conclusions: Nuss technique is an efficient method, with very good aesthetical and functional results, allowing quick social and professional patients’ reintegration, as well as an improved self-image and self confidence.

Tracheal stenosis in children, old problem, new techniques
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Tracheal stenosis is an unusual and sometimes lethal condition. Imaging: HR-CT-Thorax and volume rendering technique. With the flat detector CT it is possible to visualize the relationship between trachea and the great vessels with high spatial resolution during cardiac catheterization. During surgery, children are on the heart-lung-machine (Stockert S-5, priming volume 200ml, D 100 kids oxygenator). The tracheal surface is usually exposed via median sternotomy. In case of sliding plastics cardiopulmonary bypass (CBP) is used. Surgery is performed on the empty beating heart at 30-32°C. Two arterial cannulas are used (innominate artery and ascending aorta) in order to disconnect the innominate artery temporary from the ascending aorta. In the present of LSS a slide plasty with bronchosopic control is performed. Tracheal stenosis from external compression is released with CBP by aortopexy or resection of compressing ligaments (if additional Tracheomalacia is present an external suspension is used. In the case of ventilatory problems veno-venous-ECMO using a bilumen catheter for CO₂-elimination can be used. The postoperative care is characterized by a longer time of mechanical ventilation (up to weeks) and a difficult weaning from the respirator. A modified heart-lung-machine (Stockert S-5, Highlight 800 Oxigenator MEDOS) may be used at the ICU, if necessary. We report 3 children suffering from different types of tracheal stenosis.

Conclusion: A highly specialized team and individual management are essential for good results. No surgical technique corrects all of the anatomic variants of this disease. Long-segment tracheal stenosis is best treated using slide tracheoplasty and concomitant repair of cardiovascular lesions.

Surgical treatment of primary malignancies of trachea
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The main treatment of patients with primary malignant tumors of the trachea is endoscopic recalcanalization of the trachea lumen with stenting and radiotherapy. Radical surgery of the trachea primary malignancies is single-step circular resection with end-to-end Anastomosis.

The aim was to demonstrate that a single-step circular resection is possible when tumor extension is 45% of the trachea length, with involvement of the epiglottis subfold portion. 18 single-step circular resections were performed in patients with primary tumor of the trachea. Adenocarcinoma of the trachea was diagnosed in 13 patients, and typical carcinoid - in 5. Among them over 45% of trachea was resected in 10 patients. Localization and extension of the tumor was established by fibbron-choscopy, and MDCT. Tumor extension from 1.0 to 3.0sm was diagnosed in 8 patients, and from 3.0 to 6.0sm – in 10 patients. Single-step circular resections and tracheostomal anastomosis were performed in 7 patients, laryngotracheal anastomosis - in 6, and a laryngotracheal resections were made in 5 patients. Immediate and prospective results of the treatment are considered to be sufficient in all patients. In Pearson-Grillo laryngotracheal resection the distance between the anastomosis and vocal cords varied from 1 sm to 3 sm.

Single-step circular resection is the only radical surgical treatment of primary trachea malignancies. Subfold portion involvement is not a contraindication to a single-step circular resection of the trachea and subfold portion of the epiglottis. Postoperatively, a single-step circular resection for adenocarcinomatous cancer must be followed by radiotherapy.

Congenital tracheal diverticulum seen in adult age: Two cases
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Tracheal diverticulum is a very rare entity. Congenital ones appear 4-5 cm below the vocal cords and in right lateral wall of trachea. Usually diagnosed incidentally. We present here two tracheal diverticulum diagnosed incidentally.

Case 1: A 65-year old male patient was admitted to our clinic with back ache and cough. The CT scan of the chest showed posterior mediastinal mass and tracheal diverticulum which was in the middle of trachea at posterolateral wall. Fiberoptic bronchoscopy demonstrated the communication between the trachea and the diverticulum. The patient was operated because of posterior mediastinal mass, not considered for tracheal diverticulum.

Case 2: A 51-year-old male patient was admitted to clinic of nephrology with chronic renal failure. The patient was referred to our clinic with dyspnea. The CT scan of the chest showed pleural effusion and a tubular air-filled structure, which was adjacent to the posterolateral wall of the trachea at the level of thoracic inlet. Fiberoptic bronchoscopy demonstrated a communication between trachea and diverticulum. The patient was treated conservative management with antibiotics and bronchodilators.

Tracheal diverticulum include surgical resection and conserva-
tive management. Treatment options change depending on the patient’s symptoms, age and physical state. Surgery is recommended for symptomatic patients, conser-
vative medical treatment for elderly and debilitated patients.

Intraoperative management of tracheobronchial ruptures after double-lumen tube intubation
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Background: Tracheobronchial rupture is an uncommon but a potentially serious complication of endotracheal intubation. In this study, diagnosis and treatment strategies of a specific group of ruptures caused by double-lumen tube intubation is presented.

Methods: The medical records of 18 patients diagnosed and treated for tracheo-
bronchial rupture after double-lumen tube intubation between January 1999 and October 2010 is analyzed retrospectively.

Results: In all cases, the rupture occurred at the membranous part. The average length of the laceration was 2.44±1.78 cm. The most common localization of the rupture was at the lower third of the trachea (n=7, 39%) or at the left mainstem bronchus (n=5, 27%). One patient was diagnosed before the incision by fiberoptic bronchoscopy and 17 patients by direct vision of the rupture intraoperatively. All
patients are treated successfully with surgery. There was no any morbidty or mortality recorded related to the tracheobronchial rupture.

**Conclusions:** The thoracic surgeons must be alerted for any tracheobronchial rupture in patients that are intubated by double-lumen tube which is commonly used for thoracic operations. Immediate repair must be performed for any laceration which is diagnosed intraoperatively.

**P2412**

Perfection of diagnostic and tactic of stage-by-stage endosurgical treatment of cicatrical stenoses of a trachea

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**Background:** Research devoted to studying of complex treatment of cicatrical stenoses of trachea (CST) with use of various methods of stage-by-stage surgery including endoscopic laser photodestruction, bagging, stent insertion and tracheal resection are presented.

**Methods:** The analysis of results of diagnostics and endoscopic and surgical treatment of 101 patients with CST was made. 1 group have made of 44 (43.6%) patients at whom extent of a stenosis has made to 2 sm and 2 group have made of 57 (56.4%) patients with a long of cicatrical zone of a trachea more than 2 sm.

**Results:** After endoscopy in a case of restenosis were carried out by a following stage a circular resection at 36 patients. At 51 (50.5%) the patient endosurgical methods were independent and an effective treatment and have allowed them to avoid reconstructive surgery. At 29 (28.7%) patients endoscopic methods have served as a preparatory stage to a circular resection of a trachea. So in 1 group endoscopic method of treatment as stages of surgical corrections of CST was independent and effective at 28 (71.8%) from 39 patients, while in 2 group at 18 (36.5%) patients that is authentic twice less than in 1 group.

**Conclusion:** The diagnostic-and-treatment algorithm and tactics of combined stage-by-stage treatments with application of hi-tech methods of diagnostics and treatment depending on extent of CST is developed.

**P2413**

Evaluation of plethysmography findings as a diagnostic method for patients with post-intubation tracheal stenosis (PITS)

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**Introduction:** PITS is a serious disease can caused many diagnostic problems. It caused by cuff pressure during tracheal intubation. Generally, invasive diagnostic methods, based on fiber-optic or rigid bronchoscopy, are suggested for initial treatments.

**Aims and objectives:** This study aimed to evaluate the plethysmography findings, as a diagnostic method for PITS, and assess the relationship between plethysmography and bronchoscopy findings in patients with PITS.

**Methods:** The sample included 30 patients, who were admitted to an ICU or in a surgical ward during the course of a year and had been diagnosed with PITS. All patients after a history underwent plethysmography and then rigid bronchoscopy; and the relation between plethysmography and bronchoscopy findings was able to be examined.

**Results:** Regarding the relationship of the variables under evaluation by bronchoscopy with plethysmography findings, stricture intensity had the highest correlation with SRaw (resistance of upper airways) with a p-value = 0.001. The relationship of the length of stricture with FEV1, MEF 50 and MEF 75 was significant (P-value = 0.039, 0.042 and 0.036 respectively) in the univariate and with RV% and TLC% in the multivariate analysis.

**Conclusions:** Significant relationships were found between plethysmography and rigid bronchoscopy findings in patients with PITS; some statistical formulas were developed which allow medical practitioners additional opportunities to estimate the stricture intensity without bronchoscopy. Other significant relationships were also found - regarding the length of stricture - which affirmed the effectiveness of plethysmography for evaluation of patients with PITS.

**P2414**

Difficult intubation of the esophagus or trachea stent – When cervical muscle contractures combined with the narrowing. Descriptions of cases

Adam Rzechonch, Jerzy Kolodziej. Department of Thoracic Surgery, Medical University of Wroclaw, Wroclaw, Lower Silesia, Poland

**Purpose:** The muscle contraction is the main cause of difficulty of tracheal intubation. Self-expanding tube stents are typically placed using a rigid bronchoscope. How to do it by simultaneous occurrence of strictures and the stiff neck?

**Material:** We described 2 cases of patients with received prolonged mechanical ventilation in an intensive care unit. In both patients developed: stiff neck and tracheoesophageal fistula (TEF).

**Method:** The insertion of self-expanding stents has been found successful in both patients.

**Conclusion:** Stiff neck and narrowing of the trachea or esophagus, are a significant obstacle in the establishment of the stents. They should be taken into account in planning treatment. Use of fiberscope, guides and intubation tubes of increasing diameters is relative simple and cheap way to solve the problem.

**P2415**

Transcervical versus transternal approach of bronchial stump following pneumonectomy – Two methods in an open competition

Adrian Istrate 1, Cristian Paleru 1, Olga Danaila 1, Ciprian Lovin 2, Dan Ulmeanu 3, Ciprian Nicolae Bolca 1, Andrei Cristian Bobocca 1, Radu Serban Matuschi 1, Ion Cordes 1; 1Thoracic Surgery Clinic, National Institute of Pneumology ”Marius Nasta”, Bucharest, Romania; 2Thoracic Surgery Department, Emergency Clinical County Hospital, Galati, Romania; 3Thoracic Surgery Department, Emergency Clinical Hospital “Elia”, Bucharest, Romania

**Introduction and objectives:** Bronchial stump dehiscence after pneumonectomy was classically treated tough transternal transthoracic approach, method developed in the 60’s. In 1996, Azorin, performed first bronchial transcervical approach.

**Methods:** Between March 2001 and February 2010 in our Clinic, we performed 15 cases of transternal transthoracic approach (6 cases of left primitive bronchial fistula) and 2 cases of transcervical approach of the left bronchial stump fistula.

**Results:** In transternal transthoracic approach: M:F = 12:3. 11 neoplastic (73.57%)/4 TB empypema, 4 cases early (<30 days) fistula and 10 cases of late fistula. 1 case of pulmonary artery lesion, no mortality, fistula recurrence in one case (one line stapled bronchus). The average hospitalization was 7 days and clinical follow-up was between 2 and 56 months. The transcervical approach: M:F = 1:1, both empypema. Mean operating time was reduced to 40 minutes, related to 150 minutes of the transternal transthoracic approach, with full mobilization of the patients second day after surgery and a hospitalization of 3 days. Clinical follow-up was between 2 – 16 months.

**Conclusions:** Even that transternal approach of the bronchial fistula remain a major option, the new transcervical approach offer in selected cases an non-traumatic, non-shocking alternative, with very good result. Good experience in mediastinoscopy is required.
P2416
Efficiency of nebulised therapy in preventive maintenance of bronchial stump insufficiency after pneumonectomy
Shahrat Hashimovici1, Georgy Pahomov1,2, Rustem Hayaliev1,2, Oktarii Isroili1, Otbebek Eshonboldiezhaev1,2, Ezof Rizaevi1,2,1 Department of Surgery of Lung and Mediastimum, RSCS Named after Acad. V.Vahabov, Tashkent, Uzbekistan; 2Hospital Surgery Kafedra, Tashkent Medical Academy, Tashkent, Uzbekistan.

Introduction: Introduction for preventive maintenance COPD nebulised therapy (NT) promotes the high local activity of inhaled remedies.

Purpose: To value efficiency of NT in preventive maintenance of bronchial stump insufficiency (BSI) after pneumonectomy (PE).

Material and methods: The interests results were received at study of the in-fluence accompanying pathology on frequency of development BSI after PE. The frequent diseases were COPD and heart-vascular pathology. So from 390 patients in 207 (53.1%) accompanying COPD was revealed, on background which after PE in 36 (17.4%) patients was noted development of BSI. In turn, amongst 183 (46.9%) patients without accompanying COPD this complication was noted only in 2 patients (2.2%). Such presence of COPD raised the risk of the development BSI more then in 6 times.

Results: Introduction NT has allowed in the main group to reduce the risk of the intensification COPD to 16.1% after PE on the left and 17.2% after PE on the right, and frequency of the development of BSI on background accompanying COPD decreased to 3.2% and 6.9% accordingly. In the main group accompanying COPD was revealed in 60 patients (61.2%), activation after operation was noted in 10 (16.7%) patients, but development of BSI only in 3 patients, that has formed 5.0%.

Findings: Introduction of NT for preventive maintenance COPD promotes not only reliable improvement of the factors of breathing frequency (P <0.002) and functional respiratory tests (P <0.001), but also reduction of the frequency of the intensification of obstructive syndrome from 52.4% to 16.7% that led to reduction of the risk of development BSI from 16.5% to 5.0%.

P2417
Diagnostic surgical lung biopsy in hematologic patients with pulmonary complications
Liliyan Junker1, Jörg Halter1, Franco Gambazzi2, Daiana Stelz1, Lukas Bubendorf2, Dominik Heim1, Martin Stern2, Christoph Buecher1, Didier Lardinois1, Michael Tammen1, 1 Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital Basel, Basel, Switzerland; 2 Clinic of Hematology, University Hospital Basel, Basel, Switzerland.

Pulmonary infectious and non-infectious complications are frequent in hematologic patients with liver or persistent infectial bronchoscopiy is performed. However in a considerable number of cases bronchoscopy is inconclusive and lung tissue needed to achieve a definitive diagnosis. We assessed the diagnostic yield and risk of VATS biopsy or open lung biopsy (OLB) in hematologic patients suffering from pulmonary complications. 81 patients with a mean age of 47 years underwent VATS (73%) or OLB (27%) from 2000 to 2010. 49 patients underwent allogeneic and 7 autologous SCT, 21 had high dose chemotherapy. Examinations revealed an infectious agent in 6 (Tbc, 2 PEP, 2 bacterial, echinococcus), bronchiolitis obliterans in 23, organizing pneumonia in 8, diffuse alveolar damage in 8, NSIP in 2, and lymphoma in 3 cases.

There was no perioperative death. A prolonged ICU stay (>72hours) was observed in 11 cases. 5 of these patients were already on the ICU prior to surgery. Re-operation was needed in 6 cases. No wound infection was observed. Thorax drainage was prolonged (>5) in 12 patients (15%). One patient developed a pneumothorax 12 days after VATS during a flight. 30-day mortality was 7% (6/81): 4 diffuse alveolar damage, 1 fungal infection/renal failure and 1 OP/renal failure. 2 of the 6 deaths occurred in patients already ventilated prior to surgery.

Summary and conclusion: The diagnostic yield of lung biopsy in hematologic patients is very high directly affecting patient management. The risk of the surgical procedure itself is acceptable. Mortality is increased in patients ventilated prior to surgery and in those with diffuse alveolar damage on histology.

P2418
Lung biopsy predicts outcome in bronchiolitis obliterans following allogeneic stem cell transplantation
Andreas Holbrueder1, Jörg Halter1, Spasenija Savic1, Lukas Bubendorf1, Dominik Heim1, Martin Stern2, Christoph Buecher1, Didier Lardinois1, Michael Tammen1, 1 Clinic of Hematology, University Hospital Basel, Basel, Switzerland; 2 Department of Pathology, University Hospital Basel, Basel, Switzerland.

Graft versus Host Disease (GvHD) is a serious complication following allogeneic stem cell transplantation. Lung involvement with a decline in FEV1 is a pulmonary manifestation of GvHD which occurs in 5 to 8% of SCT recipients. Early studies showed that bronchiolitis obliterans (BO) is the histological correlate of pulmonary GvHD and associated with a high mortality. In our institution VATS biopsy is still considered the gold standard to diagnose bronchiolitis obliterans, after pulmonary infection has been excluded by BAL. In this study we analysed the histological pattern and outcome of 22 patients with biopsy proven bronchiolitis obliterans. There were no major surgical complications of VATS in this immunocompromised patient group. Twelve patients showed conspicuous bronchiolitis obliterans (CBO) on biopsy whereas there was lymphohytic bronchiolitis in 10 cases (LBO). Median duration until diagnosis was 43.6% in CBO and 62.6% in LBO. There was no difference in age, underlying hematologic disease or pretreatment between the two groups. Almost all patients suffered from chronic GvHD. Median time to the diagnosis of bronchiolitis obliterans after allogeneic SCT compared to 703 days in LBO. FEV1 markedly improved in the majority of cases with LBO whereas FEV only partly improved in patients with CBO. Six patients died in the CBO group as compared to only one death in the LBO group.

Conclusion: The histological pattern of lymphohytic bronchiolitis obliterans is associated with a much better prognosis as compared to conspicuous bronchiolitis obiterans following allogeneic stem cell transplantation. We recommend to perform VATS in patients with suspected bronchiolitis obiterans.

P2419
VATS lung biopsy is the method of choice for patients with ambiguous pulmonary pathology to establish a morphologic diagnosis
Mikle Pikunov, Yuriy Esakov, Thoracic Department, A.V. Voinozhskogo Surgery Institute, Moscow, Moscow, Russian Federation.

Objective: In spite of intensive development of diagnostic tools in pulmonology such as HRCT, PET, bronchoscopy examination peripheral lung biopsy (PLB) and interstitial lung diseases (ILD) are often require excision lung biopsy for the morphological diagnosis. We evaluate the efficiency and safety of the VATS lung biopsy in the final diagnosis for patients with ambiguous cases.

Methods: 210 patients with PLL (group I) and 87 patients with ILD (group II) were enrolled. Mean age: 54.4±2.0 y. We used HRCT for lesion(s) visualization in all cases. All patients in both groups underwent VATS lung biopsy and morphological investigation of the specimens to establish a final diagnosis.

Results: In accordance to preoperative examination in group I there were: neoplasm’s, tuberculosis and hamartomas. In the group II there were suspicions to sarcoidosis, idiopathic pulmonary fibrosis (IPF), diffuse chronic lymphogenous-oinomiatosis (LAM). Morphological diagnosis was obtained in all cases. We found benign neoplasm 39%, early forms of lung cancer in 42%, tuberculosis in 12%, metastatic disease 4.2%, carcinoid tumors in 2%, and nodal fibrosis in 5.6% of all specimens in group I. In the group II there were sarcoidosis (48%), IPF (26%), alveolitis (24%) and LAM (2%). Accuracy of preoperative examination was 91% and 66% in the first and second groups respectively.

Conclusion: VATS lung biopsy provides adequate specimen volume for morphologic diagnosis and associated with 100% diagnostic accuracy. Minimal postoperative morbidity and mortality rates are justified this procedure as a method of choice for patients with ILD and PLI.

P2420
Surgical treatment for lung metastases in patients with colorectal cancer
Adam Rzechonok, Jerzy Kolodziej, Marek Lubicz. Department of Thoracic Surgery, Medical University of Wroclaw, Wroclaw, Lower Silesia, Poland

Introduction: The paper presents a history of surgical treatment for lung metastases from colorectal cancer and subsequently an analysis of the treatment results, presenting some differences of lung metastasectomy.

Materials and methods: A review of the literature from the years 2000-2010 for the resection of metastatic tumors of colorectal cancer and our experience and results from the material of 60 patients operated in our unit in 2004-2007.

Results: Pulmonary metastasectomy of the secondary lesion of the colon gives the best results in cases of primary low pathological staging of a resectable primary colorectal cancer (T1 to T2 preferably limited to 3 number of lung metastases after a one metastasis to the liver disease in free time exceeding 12 months and the normal level of intestinal-embryonic marker (CEA). Conversely-factors pleading for the surgical resection renouncement for metastases are: medium and high degree of advanced colorectal cancer (3A-4, N1-2), multiple metastases to the lung or liver disease-free time of less than 12 months and an increase in serum CEA (above 10 ng/ml).

Conclusion: 1. Results of surgical treatment of metastatic colorectal cancer encourage a wider patient eligibility among into account prognostic factors. 2. Decisions about the way of surgical treatment for metastatic disease should be taken...
based on the assessment of the patient (organ function), number of metastases, and the value of CEA. 3. Regardless of the primary cancer focus, the G feature of differentiation, the number and size of metastases surgical resection extend patients life.

P2421
The role of VATS in the staging of non small cell lung cancer
Reza Baghiri, Zaouliah Haghj. Thoracic Surgery, Mashhad University of Medical Science, Mashhad, Islamic Republic of Iran

Introduction: One of the points discussed in NSCLC always has been to use staging method with high accuracy, including broncoscopy, CT scan, PET scan and mediastinoscopy.

Another completing method for staging is VATS. In our study we decided to evaluate diagnostic accuracy of VATS for staging of NSCLC.

Material & methods: The case series study was performed on 40 NSCLC patients from 2007 to 2010.After complete preoperation evaluations (history and physical exam, CXR, CT scan, broncoscopy, TTNB and mediastinoscopy if needed in some cases), patients without criteria of inoperability have been reevaluated with VATS staging before the surgery. Thoracotomy was performed after VATS, when we didn't have any exclusion criteria for surgical resection. We evaluated diagnostic accuracy of VATS.

Results: 40 patients were studied (M/F = 21/19), the mean age was 57 year. The most common symptom was coughing (%90). The most common finding of CT scan of the patients was mass lesion in 100% patients. The endobronchial lesion was in 29 patients. We performed bronchoscopy on 7 patients for staging because of N2 lymph node size more than 1 cm, which was negative finding for metastatic involvement. 6 patients haven't been candidates for surgical resection after pulmonary resection. VATS was performed for plural sedimentation in 2 N2 lymphatic involvement, and one for stellate lesion in other lobe. Thoracotomy was done on 34 patients. Operation was successful in 31 patients complete resection and failed in 3 patients due to hilar extension of tumor. The diagnosis accuracy of VATS was 92.5%.

Conclusion: According to high diagnostic accuracy and easy to performance of VATS we recommend it to be done before surgery.

P2422
Therapeutic pulmonary metastasectomy for colorectal cancer should be chosen in any disease-free interval, size of tumor, and carcinoembryonic antigen level
Masao Nanako. General Thoracic Surgery, Eiju General Hospital, Tokyo, Japan

Aims: We retrospectively review our experience of pulmonary resection of metastases from colorectal cancer, in order to document postoperative clinical outcome and survival.

Methods: From 2003 to 2010, in 16 patients, 19 pulmonary metastases from colorectal cancer were therapeutically resected in our hospital (9 were rectal and 7 were colon, 10 males and 6 females; mean age 66.3 years). The indication for these metastasectomies was based on Thomford’s advocacy. They were analyzed retrospectively to calculate prognosis, and reviewed to verify their disease-free interval (DFI), interval between resection of primary tumor and diagnosis of lung metastasis, size of largest resected metastasis, pre-metastasectomy carcinoembryonic antigen (CEA) level with the reported prognostic factor. After lung metastasectomy, patients were followed up for 2-95 months (median: 45.5 months).

Results: There was no operative mortality. Complications occurred 3 out of 16 patients (19%) but were major only in 1 (6%). Overall, 3- and 5-year survival rates, from the date of pulmonary metastasectomy were 78.6% and 48.1%, respectively. The mean of DFI was 19.9 months (0-99), the mean size of largest resected metastasis was 22.6mm (9-60), and the mean of pre-metastasectomy CEA level was 5.1 ng/ml (1.0-32). These factors were not associated with longer survival.

Conclusion: Based on our experience, a good prognosis can be expected after therapeutic pulmonary metastasectomy for colorectal cancer regardless of factors such as DFI, size of metastasis, pre-metastasectomy CEA level.

P2423
A rare solitary pulmonary plasmacytoma case
Hakan Kiral, Turan Ceylan, Mustafa Kupeli, Levent Alpay, Erdal Okur, Irfan Yalcinkaya. Thoracic Surgery, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

Solitary pulmonary plasmacytoma is extremely rare tumor therefore, we present a case report of such a tumor. A 61-year-old Turkish woman presented with a 10-month history of chest pain. Chest radiography showed homogenous opacity and obliteration of left costophrenic sinus. Chest computed tomography revealed a heterogeneous mass measuring 439s
Salvage lung resection for local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers

Background: Among the pneumonectomy patients we have operated, we have often faced the situation when recurrence appeared after SBRT.

Methods: We retrospectively reviewed 9 patients (3 with stageII-Inon-small cell lung cancer and 6 with metastatic lung tumors) who underwent salvage surgical resection for local recurrence after SBRT.

Results: Of the 9 patients, 7 underwent lobectomy, and the remaining 2 did bilobectomy and segmentectomy, respectively. 2 with metastatic lung tumors had pleural adhesion resulted from SBRT-related fibrosis. However, there was no case in which SBRT made surgical procedure impossible. Retrospectively considering the course after SBRT, once all 9 irradiated tumors resulted in disease progression, they grow in size rapidly.

Conclusions: We have treated all patients without major technical difficulties by SBRT-related change. SBRT did not close the door to perform salvage surgical resection, and surgical resection might be feasible for local recurrence after SBRT. However, close follow-ups are mandatory for patients treated with SBRT because tumor regrowth after SBRT is thought to occur at a rapid rate. And if patients are medically fit for surgery as the first line treatment, the use of SBRT should not be decided by only reason of its less invasiveness.

P2427

Surgical treatment of postoperative chylothorax with thoracoscopy

We studied the results of the examination and treatment of 14 patients with postoperative chylothorax for the period from 1999 to 2010. There were 11 men (78.6%) and 3 women (21.4%), the mean age was 45.5±6.4 years. Pleural effusion in all patients was one-sided, i.e. on the side of the operation.

The cause of chylothorax of all the patients was surgery in the thoracic cavity - thoracotomy with resection of the lung and mediastinal lymph dissection (8 cases), lung resection without lymph dissection (2 cases), mediastinal tumor resection (3 cases), and pneumonectomy with intrapericardial vascular root of lung (1 patient). Pleural effusion during chylothorax is rated as the milky in 6 (42.9%) cases, fester in 1 (7.1%), serous in 4 (28.6%) and hemorrhagic in 3 (21.4%) cases. The average concentration of triglycerides in the exudates was 7.1±3.2 mmol/liter. The thoracoscopy was performed to all the patients with drainage of the pleural cavity, a diet with a decrease in the amount of fat was prescribed. Total parenteral nutrition was originally required for 4 patients, and 3 patients were urged to follow it due to the ongoing chylothorax after 3-4 days. Sandostatin was included in the conservative treatment measures of 5 patients. Conservative measures were effective in 9 patients. One patient underwent pleurodesis with intrapleural injection of tetracycline/polyvinylpyrolidone complex solution. Other patients after unsuccessful conservative treatment for 7-10 days underwent thoracic lymphatic duct ligation. In the absence of the conservative measures effect, the bronchial closure is a novel option in highly selected patients. The positive factor influencing our decision were the virgin mediastinum. The dissection of the trachea through its natural route enables tracheal mobilization. It warrants minimal surgical trauma, and, if necessary, the bronchial stump has enough time to heal before the difficult pneumonectomy.

Conclusions: Video-mediastinoscopy is an alternative to the open methods as it allows approaching the left main bronchi via the mediastinum. This technique is in our choice because its specifics morbidity is minimal compared with transpericardial sternotomy or a thoracoscopic approach. The mediastinoscopic approach is a novel option in highly selected patients in order to prepare and simplify a pneumonectomy.

P2430

Value of the video assisted mediastinoscopy in the thoracic pathology – Our experience

Conclusions: The oncological thoracic pathology is growing in the last decades because of the higher exposure to the pollution and because of the higher accurate of the diagnostic. The mediastinoscopy offers the possibility of the histological histopathology and of the accurate stadialisation in every thoracic pathology.

Material and method: We retrospectively reviewed 218 patients with cervical mediastinoscopy (151 males and 67 females, mean age: 52.3 years) treated between 2008 and 2010. The indications of the cervical mediastinoscopy is indicated in table 1.

Table 1. Indications of mediastinoscopy

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected sarcoidosis</td>
<td>33</td>
<td>15.1</td>
</tr>
<tr>
<td>Suspected lymphoma</td>
<td>22</td>
<td>10.1</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathies</td>
<td>22</td>
<td>10.1</td>
</tr>
<tr>
<td>Pulmonary carcinoma</td>
<td>111</td>
<td>50.9</td>
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We biopsied at least two nodal station.

Results: The results of this procedures are indicated in table 2.

Table 2. Types of histology

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The method was not succful in four cases, which necessitated another procedures of diagnosis (thoracoscopy). For non small lung cancer the mediastinoscopy was a method of diagnosis in 79% of cases for patients contraindicated for pulmonary resection (metastasis, early respiratory disfunction, mediastinal invasion). In 18,75% of non small cancer we applied a neoadjuvant treatment with secondary resection.

There was no intra- or postoperative mortality in this material. No major bleeding necessitating further surgical occurred. There weren’t wound infection.

Conclusions: We still consider mediastinoscopy as a safe and efficient way of examining mediastinal pathology.

P2429

Five consecutive cases of left bronchial transcervical video mediastinoscopic closure

Andres Cristian Bobocca, Cristian Palovert, Olga Danaila, Adrian Istrate, Ioan Cordos. Thoracic Surgery Clinic I, “Marius Nasta” National Institute of Pneumology, Bucharest, Romania

Objective: The author reports the longest series of left bronchial transcervical closure using video-assisted mediastinoscopy, describing his experience with this technique and the particularities of the cases. Left bronchial closure as the first procedure of a two-step pneumonectomy for TB compromised lung is a rarely used technique.

Case report: Five patients, mean age of 41.5 years, two females, three males, underwent videomediastinoscopic closure of the left main bronchus in the last 14 months, two for postpneumonectomy bronchopleural fistulas and three prior to pneumonectomy in TB destructed lung. The recovery was uneventful in every case, with the patients discharged the following day. The mean operative time was 55 min. No other incidents or procedure related complications were encountered. The three pneumonectomies followed at 3-4 weeks after the bronchial closure.

Discussions: The mediastinoscopic bronchial closure is a novel option in highly selected patients. The positive factor influencing our decision were the virgin mediastinum. The dissection of the trachea through its natural route enables tracheal mobilization. It warrants minimal surgical trauma, and, if necessary, the bronchial stump has enough time to heal before the difficult pneumonectomy.

Conclusions: Video-mediastinoscopy is an alternative to the open methods as it allows approaching the left main bronchi via the mediastinum. This technique is in our choice because its specific morbidity is minimal compared with transpericardial sternotomy or a thoracoscopic approach. The mediastinoscopic approach is a novel option in highly selected patients in order to prepare and simplify a pneumonectomy.

P2426

The value of video assisted mediastinoscopy in the thoracic pathology – Our experience

Cornel Savu1, Vasile Grigorie1, Cornel Petreanu1, Nicolae Galie2, Emilia Tabac2.1 Clinic of Thoracic Surgery, National Pneumology Prof. Dr. Marius Nasta, Bucharest, Romania; 2 Clinic of Thoracic Surgery, National Institute of Pneumology Prof. Dr. Marius Nasta, Bucharest, Romania

Introduction: The oncological thoracic pathology is growing in the last decades because of the higher exposure to the pollution and because of the higher accurate of the diagnostic. The mediastinoscopy offers the possibility of the histological histopathology and of the accurate stadialisation in every thoracic pathology.

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There was no intra- or postoperative mortality in this material. No major bleeding necessitating further surgical occurred. There weren’t wound infection.

Conclusions: We still consider mediastinoscopy as a safe and efficient way of examining mediastinal pathology.
**P2431**

Spontaneous pneumothorax and Marfanoid phenotype

Veronina Maria, Govorova Svetlana, Nechaeva Galina. Therapy and Family Medicine, Omsk State Medical Academy, Omsk, Russian Federation

It well-known that the spontaneous pneumothorax (SP) and apical bullae are diagnostical criteria of a Marfan syndrome. However the Marfan syndrome is a rare pathology, and the SP at tall and thin young men meets very often. For the purpose search of features of a Marfan syndrome has been surveyed 270 patients with a primary SP. Among patients men (n=248) prevailed, middle age of patients has made 24 years.

We have analysed major and minor criterions of the Marfan syndrome in the skeletal system, ocular system, cardiovascular system, skin and integument and dura. Cleftetal major criterion met most often. Anterior chest deformity have been diagnosed for 14 patients, at 33 patients insted reduced upper-segment to lower-segment ratio or arm span to height ratio more 1.05, at 62 patients were wrist and thumb signs. Scoliosis or spondylolisthesis have been taped at 45 patients. Medial displacement of the mediastinal malloions, causing pes planus were observed at 28 patients. Sceletal minor criterias and their combinations have been diagnosed for 112 patients. Dilatation of the ascending aorta and other are not diagnosed in one case. However such minor criterias as mitral valve prolapse has been diagnosed for 125 patients. Skin and integument criterion have been diagnosed for 38 patients. Ocular and dura criterion met seldom. The combination of criterias has not allowed to diagnose Marfan phenotype at one patient, however allows to speak about presence Marfanoid phenotype at the patients with a SP. The finding of a strong association of SP with Marfanoid phenotype suggests that in many patients may be a manifestation of a systemic abnormality of connective tissue.

**P2432**

Bronchial stump insufficiency after pneumonecnotomy in purulent-destructive diseases of lungs

Shahrat Hudyayberganov1, Georgy Puhomov1, 2, Rustem Hayaliyev1, 2, Orikalli Irsyn1, Otabek Eshbonhodjaev1, 2, Sharif Rahimty1, 2. 1Department Surgery of Lungs and Medistinum, RSCS Named after Acad. V. Vahidov, Tashkent, 2Hospital Surgery Kafirda, Tashkent Medical Academy, Tashkent, Uzbekistan

As is well known, bronchial stump insufficiency (BSI), bronchopleural fistulas (BPF) and connected with them empyma pleura are the main reasons of the re-duction to efficiency of the surgical treatment of lung cancer, purulent-destructive diseases of lungs (PDDL) and other surgical pathology of thorax.

**Material and methods:** Results of complex examination and treatment of 684 patients had comparative analysed, from which 575 (84.1%) patients underwent pneumonecnotomy (PE) on cause oncological pathology or PDDL, but 109 (15.9%) patients were treated on cause BPF after PE. The average age 56.4±4.1 years. The main group has formed 98 patients, admitted for 2006-2008 and undertaken design of the surgical treatment, founded on determination of the groups of the risk of the development BSI after PE.

**Results:** The frequency BSI after PE depending on presence different factor among 87 patients with PDDL was apart considered. PE is on the right made in 25 (28.7%) patients, on the left in 62 (71.3%) patients. BSI after PE is revealed in 4 (16.0%) and 7 (11.3%) accordingly. PE on cause PDDL noted increasing of the frequency BSI from 10.5% to 12.6% (11 from 87 patients), and risk of the development of PE complications, depending on side of the operations forms - 16.0% after right-side and 11.3% after leftside PE.

**Conclusions:** In patients of oncological profile, which is planned PE, frequency of accompanying BPF forms 53.8% patient then in patients with PDDL this factor reaches 75.2%, in turn exacerbation COPD after performing PE noted in 48.8% and 63.6% patients accordingly, but risk of the development BSI on this background reaches 16.5% that requires including in the treatment nebulised therapy.

**P2433**

Congenital pulmonary airway malformation in a 10 year old male adolescent

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Congenital pulmonary airway malformation (CPAM), more commonly and previously termed congenital cystic adenomatoid malformation is an uncommon anomaly characterized by multicystic lesions due to proliferation of the respiratory bronchioles. This lung anomaly has an incidence of 1:2500-35,000 and 90% of this number occurs in children below 2 years old. Late-onset CPAM is an infrequent illness and requires a high level of suspicion. It usually presents in the form of repeated infections but very rarely remains to be asymptomatic until its diagnosis. This is a case of a previously healthy, apparently asymptomatic 10 year old male adolescent who had an incidental finding of a pulmonary bulla on chest radiograph taken while he was worked up because of a high grade fever which eventually he was diagnosed of dengue fever. He underwent elective right upper lobe lobectomy and was discharged improved on the 4th post-operative day. The final histopathology result is consistent with a congenital pulmonary airway malformation, type 1.

**P2434**

Lung tissue glue (LTG) application in lung surgery and thoracic traumas for sealing lungs tissue: Suture, bronchial stump

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Stable sealing of lungs tissue is the core principle and the key condition for positive results of postoperative recovery period after thoracic surgery. Hardest complication in thoracic surgery is the inconsistency of bronchial stump, the bronchial fistulas (15.5%). Due to this possibility of glue usage for lung surface processing with sealing effect is the most actual for thoracic surgery, as the possibility of adequate elasticity while lungs tissue elongation with minimal collateral effects.

The advantages of LTG: inexpensiveness, highly adhesiveness and hydrophilic, ability to change elasticity, viscosity, adhesiveness, high rupture strength, microbiological stability, low toxicity. In our thoracic department actively applied till September 2010 latex glue, resulted drainage period average 2-3 days after operations (in purulent-destructive processes max 5 days).

Traditionally the average drainage period more than 5-7 days, and more complications. The larger scale of application is possible but not happen due to lack of financing from our hospital administration.

**P2435**

Lung volume reduction surgery for a decompressed COPD – Case report

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**Introduction:** Lung surgery reduction is a known method which can improve the quality of life for certain COPD. Parts of the lung that are particularly damaged by empyma pneumosa are removed, allowing the remaining, relatively good lung to expand and work better.

**Clinical features:** The work presents a patient with stage IV COPD admitted in our service after a severe decompensation. Comorbidities: severe obesity, chronic corionic ischemic disease and diabetes, left pneumonitis (secondary a giant bulla of empyma pneumosa) and infectious pneumonia. We maintained the antibiotheraphy and we applied an anterior pleurectomy on the left mediooclavicular line. The evolution was initially good with suppression of the tracheotomy’s canule and of the pleurectomy’s tube in five days.

**Surgery:** 48 hours after removing the chest tube, the pneumotorsox received and we decided the surgery treatment. We performed the resection of the giant bulla and mechanical pleuradosis.

After opening of the bulla we used a fold of visceral pleura to covering the cavity in separated points.

**The outcomes:** The postoperative evolution was very good with spontaneous closure of the tracheotomy and with ablation of the tube in a week. The respiratory test indicated a improved with 15%.

**Discussion** Lung volume reduction surgery is indicated in selected cases, after surgery both lung functional tests and clinical performance of the patient beefing improved.
269. Lung transplantation

P2436
Foreign body: same clinic-diﬀerent diagnosis
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Foreign body aspiration is a serious condition with risk of mortality. It happens at all ages but mostly at childhood. Chest x-ray can demonstrate the foreign body if is in the radiopaque. But laterally and oblique chest graphs must be seen for the exact diagnosis with its size and localization. We report two cases admitted with same symptoms indicate to foreign body but different final diagnosis.

Case 1: A 1.5-year old child with Down syndrome was admitted to emergency clinic of our hospital with cough, wheezing and stridor. There was a history suitable for a foreign body aspiration and no any other significant history. Chest x-ray demonstrated an opacity similar to a foreign body. We performed a rigid bronchoscopy. There was no foreign body in his tracheobronchial system. Therewith esophagoscopy was performed under scope. Again there was no foreign body although the image was suitable to a foreign body. In the postoperative period with more detailed examination it was understood that the radiological opacity was an endovascular stent set up with angiography to carry on PDA for another cardiac disease treatment.

Case 2: A 3-year old child was admitted to our hospital with persisting cough, wheezing and stridor. Clinical history and chest x-ray demonstrated a foreign body similar to the first case. Rigid bronchoscopy was performed and a metallic foreign body (pencil bow) was extracted from left main bronchus.

History takes a great role in diagnosis of foreign body aspiration. Radiological investigation must perform to all suspected cases. Although a chest x-ray demonstrate mostly atelectasis and hyperaeration at the affected side a normal graph cannot eliminate the foreign body. If the suspicion persists we must apply esophagoscopy.

P2437
LSC 2011 Abstract: T helper cell involvement in COPD and lung transplantation patients
Marieke Paans, Ingrid Bergen, Menno van der Eerden, Bernt van den Blink, Peter van Hal, Nicole van Besouw, Carla Baan, Henk Hoogsteden, Rudi Hendriks. Department of Pulmonary Medicine, Erasmus Medical Center, Rotterdam, Netherlands; Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands

Background: COPD is associated with airway and systemic inflammation and end stage disease is a major indication for lung transplantation (LTx). The novel T helper 17 (Th17) subset was recently implicated in the pathogenesis of COPD and is also associated with allergen rejection. To date, little is known about the cytokine profile of circulating T cells in COPD patients.

Aim: To determine the cytokine profile of circulating T cells in patients with COPD and in stable LTx patients.

Methods: Peripheral blood mononuclear cells of COPD patients, before and 1 year after LTx and of healthy controls were shortly stimulated in vitro and T cells were analysed by flow cytometry for intracellular cytokine production.

Results: We found no differences in proportions of Th17 cytokines (IL17A, IL22, IL17F) in stable COPD patients when compared to healthy controls. In the LTx patients, proportions of IFNγ and TNFα producing T cells did not diﬀer from those in healthy controls. However, IL22 production by CD4+ and CD8+ T-cells was increased in LTx patients. Also, an increase in the proportions of IL17+IL22+ and IL17+IFNγ+ double positive T cells was found in stable LTx patients when compared with healthy controls.

Conclusions: Remarkably, T cells of LTx patients have the capacity to produce high levels of proinflamatory cytokines despite immunosuppressive drug treatment. In particular, IL22+ T cells and specific populations of IL17+ cells co-expressing IL22 or IFNγ are high in LTx patients, while IFNγ and TNFα single positive Th helper cells are not increased. These findings indicate that although general inflammatory state but that specific Th17-linked subpopulations may play a role in stable LTx patients.

P2438
Comparison between referral and explant diagnoses in lung transplant recipients: Discrepancies and additional findings
Peter Jakš 1, Mai-Britt Ernst 1, Axel Scheed 1, Silvana Geleff 2, Gerhard Dekan 2, Walter Klepetko 1, Thomas Klepetko 1, Thoracic Surgery, Medical University of Vienna, Vienna, Austria; 1Clinical Institute of Pathology, Medical University of Vienna, Vienna, Austria

Background: LTx is an accepted therapeutic option for a range of pulmonary conditions in which the diagnosis is often based on clinical data or on limited biopsy material. PostTx complications and recurrence of underlying disease may be related to the primary disease, and an accurate diagnosis is therefore essential.

Methods: A pathologic review was performed on 1056 primary LTx over a period of 22 years (1998 to 2010). Diagnoses of native lungs were compared with referral diagnoses to assess the presence of discrepancies or expanded results (malignancies or infections).

Results: 73 (7%) cases presented a different or expanded diagnosis. Discrepancies were found in 34 of 1054 cases (3%). The highest percentage of discordance was depicted in COPD (12 of 344), with the final diagnosis of UIP (n=4), chronic interstitial fibrosis (n=4), LAM (n=1) and sarcoidosis (n=1), 16 patients who were referred with the diagnosis of an interstitial lung disease had predominantly emphysema (n=12), bronchiectasis (n=2) and IX (n=2). Expanded results included Aspergillus (n=11) and mycobacterial (n= 16) infections, carcinomas (n=10), cystic adenomatoid dysplasia (n=1) and carcinoid (n=1). However, short- and long-term survival was not different in patients with different diagnoses, malignancies or implanted infections. Interestingly all mycobacterial infections and all malignancies occurred in patients with COPD.

Conclusions: On account of this high rate of discrepancies and its possible influence on survival, frequent repeated thoracoscopic investigations should be performed during the waiting list period.

P2439
Mortality in idiopathic pulmonary ﬁbrosis (IPF) on the waiting list for lung transplantation in the Netherlands
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Background: Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease with a five-year prognosis of 2.5 to 5 years. IPF is not responsive to medical treatment and lung transplantation is the only therapeutic option to prolong life.

Objective: The aim of this study was to examine waiting list mortality of IPF in the Netherlands.

Methods: Data were retrospectively collected from September 1989 until June 2010 of all IPF patients registered for lung transplantation in the Netherlands. Patients were included after revision of the diagnosis based on the IPF criteria set by the ATS/ERS. Clinical data and lung function measurements were collected at the time of screening.

Results: 167 IPF patients were referred for lung transplantation. After evaluation for contraindications and screening, 90 patients were listed for lung transplantation. During the waiting list period 33.3% of IPF patients (n=30) died compared to 13.6% in Cystic Fibrosis (CF) (p = 0.0018) and 16.3% in Chronic Obstructive Pulmonary Disease (COPD) (p = 0.003). Analysis of lung function showed a mean FVC%-predicted of 51.1% (SD 19.0) and mean DLco%-predicted of 27.1% (SD 9.4) at time of screening. Five patients were taken off the list due to new comorbidities and deterioration of physical condition, 51 were transplanted and 4 IPF patients were still on the waiting list.

Conclusions: This study revealed a significantly higher waiting list mortality for IPF compared to COPD and CF. DLco%-predicted at time of screening was considerably lower than international guidelines for lung transplantation. This indicates that timing of referral of IPF for lung transplantation can be improved.

P2440
The impact of resistant bacteria in respiratory secretions on the outcome of lung transplantation
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Introduction: Antibiotic treatment may cause growth of resistant bacteria in respiratory secretions. We assessed the association between antibiotic treatment of lung transplant recipients and acquisition of quinolone resistant gram negative bacteria (QR-GNB), and the impact of such colonization on mortality and lung rejection (BOS).

Methods: We examined data from lung transplant recipients for antibiotic treat- ment, GNB in respiratory secretions, BOS, and mortality.

Results: 126 patients were included. Median percentage of days with antibiotics was 2.8% in patients with no growth, 11.1% in patients with quinolone sensitive GNB (QS-GNB), and 26% in patients with QR-GNB. Age adjusted mortality hazard ratio was 9.2 (95% CI, 1.27-78.9) for patients with QR-GNB compared with QS-GNB. Age adjusted hazard ratios for BOS were: 3.6 (1.1-11.6) for QR-GNB compared with no growth, and 3.7 (1.33-10.3) for QR-GNB compared with QS-GNB.
Conclusions: Antibiotic treatment was associated with QR-GNB. Airway colonisation with QR-GNB was associated with mortality and with BOS. We suggest that narrow spectrum antibiotics should be preferred in lung transplant recipients. P2441 Anxiety, depression and coping in patients awaiting lung transplantation Torunn Stavnes Soyseth1, Aasta Hedal2, Gro Kil i Haugstad3, Vidar Soyseth4, Oystein Bjortuf t2, May Brit Lund3. 1Department of Respiratory Medicine,Division of Cardiovascular and Respiratory Medicine and Surgery, Ri kshospitalet, Oslo University Hospital, Oslo, Norway; 2Department of Neuropsychiatry and Psycho somatic Medicine,Division of Clinical Neuroscience, Ri kshospitalet, Oslo University Hospital, Oslo, Norway; 3Department of Mensendieck (Physiotherapy), Faculty of Health Sciences, Oslo University College, Oslo, Norway; 4Department of Respiratory Medicine, Akerh us University Hospital, Lorensk og, Norway

Knowledge is scarce about the mental aspects of living with terminal lung disease. We aimed to assess anxiety, depression and coping in patients waiting for lung transplantation.

Material and methods: A national cohort of 121 consecutive patients were evaluated by psychiatric instruments, Hospital Anxiety and Depression Scale (HAD) and General Health Questionnaire (GHQ). 89 (45 females) had COPD, 18 (9 females) fibrosis, and 14 (8 females) various other lung diseases. Mean (SD) age was respectively 56 (5), 52 (6) and 46 (8) years. Patients with cystic fibrosis were excluded.

Results: See table.

<table>
<thead>
<tr>
<th>COPD (n=49)</th>
<th>Fibrosis (n=18)</th>
<th>Other (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD Anxiety</td>
<td>4.8 (4.0)</td>
<td>3.2 (3.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>3.0 (3.0)</td>
<td>2.2 (1.9)</td>
</tr>
<tr>
<td>GHQ Anxiety</td>
<td>0.81 (0.49)</td>
<td>0.71 (0.54)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.61 (0.51)</td>
<td>0.47 (0.28)</td>
</tr>
<tr>
<td>Restrained coping</td>
<td>0.69 (0.32)</td>
<td>0.69 (0.29)</td>
</tr>
</tbody>
</table>

For all groups, mean values were within the normal range. However, the ranges were wide. Males tended to be more depressive than females (mean (SD) HAD score 4.1 (3.0) vs 3.1 (2.5), p=0.07), and have higher restrained coping scores than females (mean (SD) GHQ score 1.05 (0.05) vs 0.93 (0.05), p=0.038). The association between anxiety and restrained coping was highly significant, p=0.0001 as well as the association between depression and restrained coping, p=0.0001.

Conclusions: The strong association between anxiety and depression and restrained coping may be of clinical relevance after transplantation. Males may be more vulnerable than females in this respect.

P2442 Significance of a spirometric obstructive pattern immediately after lung transplantation Hendrik Suhling1, Jessica Rademacher1, Tobias Welte1, Gregor Warnecke2, Sabine Detterm1, Jens Gottlieb1. 1Dept. of Pulmonary Medicine, Hannover Medical School, Hannover, Germany; 2Dept. of Cardiorthoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany; 3Dept. of Radiology, Hannover Medical School, Hannover, Germany

To increase the donor pool, cadaveric lungs with extended donor criteria are increasingly accepted for lung transplantation.

In this study the impact and outcome of lung transplant recipients with an obstructive spirometric pattern as possible indicator of structural damaged lungs immediately after lung transplantations was investigated.

Analyzing all patients undergoing double lung transplantation between 1.09.2007 and 01.10.2009, we separated patients with obstructive (FEV1/VC < 0.7) and a non-obstructive pattern (FEV1/VC > 0.7) in pulmonary function tests 3 months after transplantation. Pulmonary function measurement including body plethysmography, bronchoscopy, laboratory parameter, CT and outcome was analyzed up to 36 months after transplantation.

From 122 recipients included, 17 (14%) were identified with an obstructive pattern, these were older at transplantation and had a lower donor oxygenation index and significant higher TLC. Obstructive patients developed peak FEV1 earlier after LTx and developed significantly more frequently bronchiolitis obliterans syndrome (47% vs. 14%).

Obstructive lung function pattern is associated with earlier development of BOS and might worsen the outcome after double lung transplantation. The OP in association with increase TLC and donor history suggests that the obstruction was of donor origin.

Factors like smoking status, age of the donor lung and FEV2 were indicators of a later obstructive pattern in recipients.

P2443 Probe-based confocal laser endomicroscopy in acute lung allograft rejection Jonas Yserbyt1, Christophe Dooons1, Wim Janssens1, Geert Verleden1, Vincent Ninane2, Marc Decramer3. 1Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium; 2Respiratory Diseases, CHU Saint-Pierre, Brussels, Belgium

Several aspects of normal alveolar tissue in probe-based confocal laser endomicroscopy (pCLE) have been elucidated: a description of the alveoloscapic findings in different pulmonary disorders is still largely lacking.

In a prospective study, we evaluated 40 lung transplant recipients using probe-based confocal laser endomicroscopy (pCLE) preceding BAL and bronchial lung biopsy (TLB) during bronchoscopy. In 6 patients (15%) acute rejection (AR) was diagnosed using TLB. The recordings of the pCLE images were digitally processed and analyzed for the following parameters: alveolar duct diameter, alveolar elastin thickness, macrophage diameter, number of macrophages per microscopic field and quantification of the autofluorescence signal of macrophages.

In 5 out of 6 AR cases, a diffuse infiltration of autofluorescent cells with a mean diameter of 26 ± 13 μm, was recognized in all examined segments. The number of macrophages per microscopic field and their autofluorescence intensity were significantly higher in the AR group than in the non-AR group (p < 0.001 and p = 0.03 respectively).

In all affected segments there appeared to be more than 100 cells per microscopic field, frequently presenting as clustering cells. The elastin network in the alveolar ducts of AR appeared to be of a normal architecture (alveolar elastin thickness mean 8.3 ± 4.9 μm, alveolar mouth diameter mean 371 ± 131 μm), and did not differ from the patient group without AR (7.8 ± 3.7 μm and 323 ± 89 μm, respectively).

In the lung transplant recipient group studied, our preliminary findings suggest that pCLE is able to detect an alveoloscapic pattern that might correlate with AR.

References

P2444 Frequency and characteristics of prolonged viral shedding of influenza A/H1N1 virus in lung transplant recipients Macé M. Schuurmans, Alice Zuercher, Gabriele M. Tini, Gregory Fretz, Christian Benden, Erich W. Russi, Annette Boehlert. Pulmonology, University Hospital, Zurich, Switzerland

Infection in lung transplant recipients (LTR) because it potentially triggers allograft rejection. Prolonged viral shedding (PVS) is defined as positive detection of influenza A/H1N1 virus (H1N1) by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) at day 7 or later after diagnosis. The aim was to quantify and characterise PVS of H1N1 infections among LTR in consecutive influenza seasons.

Methods: Influenza vaccination is routinely offered at follow-up visits in our outpatient clinic. LTR are also instructed to contact and visit our clinic when signs of infection occur or home lung function deteriorates 10% or more. We then frequently perform nasopharyngeal swabs (NPS) for viral and bacterial analysis.

In 2009-2010, 10 LTR were included, in whom we found positive NPS for influenza A/H1N1 virus (H1N1) by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) at day 7 or later after diagnosis, in 7 of these 10 patients (70%). PVS was defined as positive detection of influenza A/H1N1 virus (H1N1) by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) at day 7 or later after diagnosis. The aim was to quantify and characterise PVS of H1N1 infections among LTR in consecutive influenza seasons.

Methods: Influenza vaccination is routinely offered at follow-up visits in our outpatient clinic. LTR are also instructed to contact and visit our clinic when signs of infection occur or home lung function deteriorates 10% or more. We then frequently perform nasopharyngeal swabs (NPS) for viral and bacterial analysis.

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case of suggestive symptoms for influenza infection we start oseltamivir (Tamiflu) and moxifloxacin treatment pending NPS results. For proven H1N1 infection we continued treatment until weekly NPS return negative.

**Results:** In winter 2009/2010 7 patients had H1N1 infection of which 2 had PVS (28%). No serious complication occurred. 2/7 LTR were vaccinated for H1N1. For 2010/2011 we have so far documented 11 H1N1 infections and PVS in 8 LTR (73%). All LTR were vaccinated with at least 1 dose containing H1N1. Three LTR were hospitalised. 5 LTR had PVS for 2-6 weeks. Quantification of viral results and drug resistance testing are being performed. Influenza B was detected in 4 other LTR.

**Conclusion:** In this ongoing study we report an increase in frequency of PVS for H1N1 infections in LTR from 28 to 73% in consecutive influenza seasons. Most infections occurred despite vaccination and had a favourable outcome rarely requiring hospitalisation.

**P2445**

Opto-electronic plethysmographic study of the chest volume changes after lung transplantation

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**Background:** Lung transplantation is the established surgical therapy for pulmonary end-stage disease.

**Aims:** Even though the pulmonary function after lung transplantation is well studied, the chest volume changes remain uninvestigated. The aim of the study was to examine such changes by the opto-electronic plethysmography (OEP), a non-invasive technology.

**Methods:** Seven patients with end-stage pulmonary disease were studied before and after lung transplantation by OEP during quiet and forced breathing. Standard pulmonary function tests were also obtained. Three patients with pulmonary fibrosis had single lung transplantation and four patients with cystic fibrosis had bilateral.

**Result:** The functional tests demonstrated increasing in pulmonary function (e.g. FEV1% from 44±6 to 83±6). After bilateral transplantation, the OEP revealed a volume rearrangement: a decrease was noted in functional residual capacity (FRC: -2.1±1.3L), in vital capacity (-1.1±1L), in total lung capacity (-2.59±1.6L). The chest wall volume reduction was different in the upper thorax, lower thorax and abdominal compartment (e.g. FRC: -0.68L, -0.13L -1.59L respectively). After single lung transplantation the pattern was similar but less evident.

**Conclusions:** This first, preliminary, study of the chest wall volume changes reveals a rearrangement of such volumes after single or double lung transplantation. Facing the dramatic improvement in spirometric value, OEP recorded a decrease in volume parameters; such decreases were inhomogeneous through the body compartment, privileging the abdomen. Further studies are needed to better understand the value of these findings and their clinical impact.

**P2446**

Lung transplantation for pulmonary silicosis: The Israeli scene

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**Background:** Silicosis is a rare indication for lung transplantation. The number of patients with silicosis in Israel is increasing due to improper processing of a new quarz stone Caesarstone.

**Methods and materials:** We retrospectively reviewed the files of patients that underwent LT for silicosis. There were more patients transplanted for silicosis in 2009/2010 compared to the ISHLT (p=0.01).

**Results:** In winter 2009/2010 7 patients had H1N1 infection of which 2 had PVS (28%). No serious complication occurred. 2/7 LTR were vaccinated for H1N1. For 2010/2011 we have so far documented 11 H1N1 infections and PVS in 8 LTR (73%). All LTR were vaccinated with at least 1 dose containing H1N1. Three LTR were hospitalised. 5 LTR had PVS for 2-6 weeks. Quantification of viral results and drug resistance testing are being performed. Influenza B was detected in 4 other LTR.

**Conclusion:** In this ongoing study we report an increase in frequency of PVS for H1N1 infections in LTR from 28 to 73% in consecutive influenza seasons. Most infections occurred despite vaccination and had a favourable outcome rarely requiring hospitalisation.

**P2447**

Donor and recipient parameters affecting 1-year follow-up after lung transplant: Padova experience

Elisabetta Ballestro1, Emanuela Rossi1, Francesca Lunardi2, Giuseppe Marralli3, Monica Loy1, Francesco Di Chiara1, Fiorella Calabrese2, Federico Rea3, 1Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; 2Department of Diagnostic Medical Sciences and Special Therapies, University of Padova, Padova, Italy

The critical shortage of donor lungs suitable for transplant significantly limits the number of potential recipients. Many questions regarding donor acceptability still remain unanswered. Regarding recipients, less is known about peri-operative factors affecting 1-year survival. To investigate how multiple risk factors influence short term survival we retrospectively reviewed clinical data of donors and their recipients, transplanted in our centre.

We collected data from donors (n=174, mean age 35.7±10) focusing on age, Body Mass Index (BMI), orotracheal intubation (OTI) duration, marginality, cause of death, tracheal secretions and selected clinical information from their recipients (n= 200, mean age 46.8±10): native disease, BMI, type of transplant, intensive care unit (ICU) stay and OTI duration.

Donor age, above 35 yrs, and overweight (BMI>25) were independent predictors of survival less 1 year (respectively p=0.004; p = 0.05). Instead OTI duration (> 3 days), marginality, death for traumatic/cardiovascular cause, presence of tracheal secretions did not affect survival (respectively p(0.73,p=0.92,p=0.37,p=0.40; p=0.40). Concerning recipients, BMI between 18 to 20 (p=0.04) and age under 50yrs (p=0.005) predisposes to longer survival. Prolonged ICU stay (>20 days,p=0.007) and OTI duration (>3 days,p=0.0001) negatively affect short survival.

Our data suggest that some peri-operative donor characteristics do not affect short survival and might help maximize lung availability from donor pool. Recipient evaluation confirm how crucial is to reduce OTI duration which, in our study, have influenced 1year survival.

**P2448**

Clinical outcomes in patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing lung transplantation

Elisabetta Balestrio1, Emanuela Rossi 1, Francesca Lunardi 2, Giuseppe Marralli 3, Monica Loy1, Francesco Di Chiara1, Fiorella Calabrese2, Federico Rea3, 1Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; 2Department of Diagnostic Medical Sciences and Special Therapies, University of Padova, Padova, Italy

Patients with an acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) have extremely poor prognosis. Lung transplantation (LT) is not routinely performed in...
In severe delayed graft dysfunction refractory to mechanical ventilation, rhinovirus on viral PCR. Mean length of stay in ITU was 56.2 days of ECMO support was 9.2 days. Some patients had abnormal radiological changes that persisted after discharge. Mean duration of ECMO was 78.6% for the AE-IPF and 77.8% for the IPF group, respectively (p = 0.865).

In this cohort, similar clinical outcomes were observed in patients undergoing LT for AE-IPF and IPF. LT may be a viable option in patients with AE-IPF.

Conclusion: In our model, CO arises during emergency phase and its concentration is not changed by low or high CO level in ambient air. Thus, we are able to quantify CO produced by the lungs.

P2452 BODE Index as a predictor of survival in lung transplantation
Pilar Sanjuan, Isabel Otero, Pedro J. Marcos, Héctor Verea. Respiratory, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the most frequent indications for lung transplantation (LTX), but survival benefit is still under debate. We analysed the survival impact of LTX in COPD using the BODE (body mass index, airway obstruction, dyspnoea, exercise capacity) index.

Aims: The aim of our study was to analyse the survival impact of lung transplantation in COPD patients. We compared the post-transplant survival with the survival predicted by the BODE index as measured during pre-transplant clinical evaluation.

Methods: Retrospective review of 59 consecutive lung transplants performed for COPD in our centre between June 1st 1999 and December 30th 2010. The pre-transplant BODE score was calculated for each patient. Predicted and observed post-transplant survival was then compared.

Results: 59 COPD patients were analyzed. Mean age was 57.6 ± 8.1 years, 51 (86%) men, 52 (88%) patients had a BODE > 7 and 7 (11.9%) < 7. The overall survival time was 70.82 months ± 8.1. BODE > 7 had a overall survival time of 19.5 and BODE > 7 was 73.2 ± 8.6. In the subgroups with a BODE score > 7 and < 7, the 5-year survival was 75% in the BODE > 7 and 57% ± 20% in the BODE < 7 group.

Conclusions: The results of this study showed a significant survival benefit of LTX in our cohort of COPD patients. Patients with BODE ≥ 7 will be the ones who benefit the most from the procedure.

P2455 Early development of posterior reversible encephalopathy syndrome post lung transplantation
Letizia Corinna Morlacchi, Valeria Rossetti, Marta DiPasquale, Giulia Salomoni, Maria Pappalettera, Paolo Tarasi. Dipartimento ToracicoPulmonare e CardioCircolatorio, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy

Tacrolimus is a calcineurin inhibitor and has been proven highly effective in preventing graft rejection after transplantation of solid organs. Its major adverse effects are nephrotoxicity and neurotoxicity: the most severe form of the latter is PRES (Posterior Reversible Encephalopathy Syndrome).

We here describe a case of PRES in a 26-year-old woman, 5 days after she received bilateral lung transplantation for cystic fibrosis. She had been administered tacrolimus since the transplantation was performed. While in ICU, she suddenly developed mental status alterations, acute pulmonary deterioration and hypercapnia, with need of mechanical ventilation. A head CT scan and MR were performed, detecting subcortical white matter lesions and patchy, bilaterally symmetric areas of abnormally increased signal on the T1-weighted images within the cerebellum and the occipital-parietal and frontal regions of the brain: a minor alteration was also present in the thalamus. ADC (i.e. Apparent Diffusion Coefficients) mapping showed wide areas of vasogenic and cytotoxic edema.

Tacrolimus was immediately stopped and cyclosporine was introduced: her symptoms promptly improved.

A MRI was repeated two weeks later, documenting a significant improvement both of the cerebellum and the thalamus.

A follow up MRI was performed two months after the transplantation: prior lesions had almost completely resolved.

She still suffers from minor neuro-cognitive deficits (concerning calculus and short-term memory) and visual disturbances.

This case maybe significant in order to better understand the clinical features of PRES, which may present at a very early stage of tacrolimus regimen and is a generally reversible condition.
270. Aetiology, diagnosis and outcomes in community-acquired pneumonia

P2455
Characterization of a population referred to a lung transplantation centre in Lisbon
Sofia Grandeiro1, Alexandra Borba1, Luisa Sodédo3, Miguel Araujo1, João Cardoso1, Fernando Martelos2, Joana Fragata2, 1Pneumology Department, Hospital de Santa Marta, Lisbon, Portugal; 2Thoracic Surgery Department, Hospital de Santa Marta, Lisbon, Portugal

Introduction: Lung transplantation is the therapeutic option for patients with end stage lung disease. An appropriate referral contributes to a better post surgery survival.

Purpose: Characterization of the patients referred to the only lung transplantation centre in Portugal.

Material and method: The authors evaluated patients referred from January 2008 to December 2010. The following data was determined: demographics, lung disease and evaluation result. Reasons for refusal were also analyzed.

Results: A total of 199 patients were referred (51% male), with an average age of 45.5 years (range 11 to 69). Thirty per cent had the diagnosis of terminal lung fibrosis, 21% COPD, 13% cystic fibrosis, 12% bronchiectasis and the last 23% other diagnosis. After evaluation 24.6% of patients were accepted (49 patients, 25% of which already transplanted and 5 died on waiting list) and 54.3% were refused, most due to severe cardiac impairment or very poor general condition. Of the remaining patients, 9.5% are under current evaluation, 6.5% present a relative contraindication and 5% still don’t meet criteria for transplantation.

Conclusion: Despite the considerable number of patients referred, only 45.7% were eligible for lung transplant. The important number of patients refused due to medical contraindications should alert the attending physicians for an earlier referral.

P2456
Effect of BIPAP on diaphragm paralysis after single lung transplantation
Shadi Shafagh1, Parisa Adam2, Atefeh Fakhrarian1, Amir Hassan Nassin1, Fariba Ghorbani1, Neyaz Shahabedin Mohammadi3, Hamid Reza Khodam Veshk3, Katayoun Najatizadeh1, 1Thoracic Transplantation Research Center, National Research Institute of TB and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran; 2Chronic Respiratory Disease Research Center, National Research Institute of TB and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran; 3Department of Internal Medicine, Cardio-Pneumologic Hospital, Lyon, France

Diaphragm is a chief muscle of inspiration and its unilateral or bilateral paralysis can lead to dyspnea and affect ventilator function. Here, we are reporting management of an emphysematous patient who is undergone single lung transplant and was suffering from diaphragmatic paralysis.

A 53 year old male emphysematous patient was transplanted in 2009 and had no significant complication after transplantation. He was admitted 3 months and 9 months after transplantation due to acute rejection and received corticosteroid pulse therapy which the results were acceptable. 14 months after transplantation an elevated hemidiaphragm on chest x-ray was suggestive of diaphragmatic paralysis which was confirmed by paradoxical upward movement of right hemidiaphragm during fluoroscopic imaging. He had dyspnea with minimal exercise, reduced pulmonal function test (FVC from 63% to 38%) and oxygen saturation fall to 75% in rest without any oxygen supplement. Considering hypoaxia and C02 retention, polysomnography was performed to look for sleep apnea. Patient apnea hypopnea index (AHI) was 17 with 5 hypopnea, 5 central and 7 obstructive sleep events. After titration test, bi-level positive airway pressure apparatus (BIPAP)(P1=15, PE=11, st back up=14) was administered by oronasal mask. Although the authors worried about over expansion of high compliance emphysematous native lung with using BIPAP, pulmonary function test result improved significantly (FVC from 38% to 58%) and oxygen saturation during exercise increased to greater than 88% dramatically without expanding the native lung. We claim that BIPAP could be recommended for management of these patients without any considerable side effects.

P2457
Late-breaking abstract: The differences in clinical presentations between severe health care-associated pneumonia and severe community-acquired pneumonia: A single center experience
Gooheyon Hong, Sang-Won Um, Won-Jung Koh, Goo-Young Suh, Man-Pyo Chung, Ho-Joong Kim, O-Jung Kwon, Kyeong-Man Jeon, Medicine, Division of Pulmonary and Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Health care associated pneumonia (HCAP) has been proposed as a new category of respiratory infection. HCAP shows higher mortality rates than CAP. But it is not clear whether the poor outcome of HCAP is related to the presence of more comorbidities or to a higher incidence of MDR pathogen and inappropriate empirical antibiotic treatment. Thus, we aim to establish whether differences in outcomes for HCAP are due to differences in severity of pneumonia, not due to MDR pathogen. We conducted a retrospective observational study of patients with severe HCAP and severe CAP who were hospitalized through the emergency department in Jan 2008 Dec 2009 at Samsung Medical Center, Seoul, Korea, and compared clinical characteristics, severity, distribution of pathogen, and outcomes.

In total, 757 patients hospitalized with pneumonia were eligible, 382 patients were severe pneumonia. Despite the considerable number of patients referred, only 45.7% were eligible for lung transplant. The important number of patients refused due to medical contraindications should alert the attending physicians for an earlier referral.

Conclusion: Despite the considerable number of patients referred, only 45.7% were eligible for lung transplant. The important number of patients refused due to medical contraindications should alert the attending physicians for an earlier referral.

P2458
Viral aetiology and clinical characteristics of community-acquired pneumonia in adults in Guangzhou, China
Yang-Qing Zhan1, Rong-Chang Chen1, Z-Feng Yang1, 1Respiratory Medicine, The First Affiliated Hospital of Guangzhou Medical College, State Key Laboratory of Respiratory Disease (Guangzhou Medical University, China), Guangzhou, Guangdong, China; 2Faculty of Chinese Medicine, Macau University of Science and Technology, Macau SAR, China

Background: Recently epidemiological surveillance shows that viral pneumonia is more commonly reported than previously estimated. However, to date, little information is available in China.

Objective: To estimate incidence of adult viral Community-acquired pneumonia (CAP).

Methods: Consecutive adult patients with a diagnosis of CAP during April and December of 2009 were prospectively enrolled. Paired sera were routinely performed by hemagglutination inhibition assay or indirect immunofluorescence. Swab samples were tested for respiratory viruses by using virus culture and RT-PCR.

Viral aetiology was considered definite if at least one of the above tests was positive.

Results: Overall 149 CAP patients were enrolled, with 84 males. The median (interquartile range, IQR) ages were 60 (35–77) years. Paired sera were available in 70 cases. Viral aetiology was established in 48 cases (32.2%). Forty-four patients were infected by a single virus (influenza A 24 cases, influenza B 5 cases, parainfluenza virus type 3 (PIV-3) 11 cases, PIV-1 and adenovirus 2 cases each) and four cases by two viruses. Fever (≥39°C (66.7%), fatigue (64.6%), paroxysmal spasm (52.1%), sore throat (45.8%), dysnea (41.7%) and coryza (41.7%) were the most common symptoms in viral pneumonia patients. Some influenza A or PIV-3 infected patients manifested hemoptysis and chest pain. Dysnea and gastrointestinal symptoms were also common in influenza and PIV-3 infected patients. Oxygen therapy was more common in viral pneumonia patients than others (54.2% vs 31.7%, P=0.008).

Conclusion: Respiratory viruses were common pathogens in CAP in Guangzhou.

P2459
Pneumonia in patients who received health care at home – Should they be categorized as CAP or HCAP?
Toru Rikimaru, Noriko Hakushima, Reiko Toda. Department of Respiratory Disease, Fukuoka Sanno Hospital, Fukuoka City, Fukuoka Prefecture, Japan

Introduction: Healthcare-associated pneumonia (HCAP) is a condition in patients (pts) who are not hospitalized but features are similar to hospital-acquired pneumonia. There are many people who receive HC at home instead of at a nursing home (NH). It is not clear whether they should be treated as community-acquired pneumonia (CAP) or HCAP.

Aims and objectives: This study sought to declare the features in pts who received...
HC-at-home, and to classify them as CAP or HCAP by comparing them with CAP and NH-acquired pneumonia (NHPA) which occupy an important position in EP.

Methods: We evaluated and separated 1000 pts into three groups, Group A 517 pts; complete CAP (A), Group B 333 pts; NHPA (B), and Group C 160 pts; who received HC at home (C).

Results: The features of C were similar to B in age, and between A and B in sex, total protein and independency. There were no differences between the three groups in body temperature, WBC and CRP. In bacteriological features, S. pneumoniae, H. influenzae and K. pneumoniae were 9.5%, 5.8% and 3.9% in A, 7.2%, 2.2% and 10.9% in B and 3.6%, 5.5% and 9.1% in C, respectively. Other features of B and C were similar and had many drug-resistant pathogens e.g. MRSA (A: 5.3%, B: 21.0%, C: 16.4%) and P. aeruginosa (A: 2.5%, B: 13.4%, C: 10.9%). Mortality rates of A, B and C were 6.0%, 18.6% and 10.0%, respectively.

Conclusions: The clinical features of C were similar to NHPA in many categories. We concluded that pneumonia in pts who have received HC at home should be classified as HCAP, especially in poor independency pts.

P2460
Role of viruses, alone and in association with bacteria, in adults hospitalized with community-acquired pneumonia (CAP)
Elisa Mincholé1, Sergio Fandos1, Ana Lasierra 2, Ana Lilian Simon 1, María Angeles Ruiz 1, Cruz Villuendas3, Elena Foret1, Salvador Bello 1, Paloma Sáez-Cano 1, María Alfonso1, Marta Inchausti 1, Beatriz Gómez 1, Nuria Marina 1, Luis Alberto Ruiz 1, Ainhoa Gómez 1, Sandra Pedrero 1, Iratxe Seijas 2, Rafael Zakacain 1, 1Pneumology, Cruces Hospital, Barakaldo, Spain; 2Intensive Care Unit, Cruces Hospital, Barakaldo, Spain

We performed a prospective, observational study of etiology of community-acquired pneumonia (CAP) admitted in our hospital, including bacteria, viruses and mixed bacteria/virus cases. From 228 patients, we carried out a complete microbiological searching, including spuit, urinary antigens, hemocultures, paired serologies, as well as viral immunofluorescence, and two PCR for respiratory viruses from nasopharyngeal washes.

At least one etiological agent was identified in 155 patients (67.98%). Fifty seven (36.7%) were typical bacterial CAP, 57 viral (or atypical bacterial) (36.7%) and 41 (26.4%) mixed (virus and bacterial). (Table 1)

Table 1. Etiology of CAP patients

<table>
<thead>
<tr>
<th>Table 1. Etiology of CAP patients</th>
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<tbody>
<tr>
<td><strong>Viral</strong> (Altogether)</td>
</tr>
<tr>
<td>35</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
</tr>
<tr>
<td>155</td>
</tr>
<tr>
<td>100%</td>
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</tbody>
</table>

Conclusions:

- Viruses are very common agents in hospitalized adults with CAP, being present in more than half of the cases of well-known etiology, and in one out of three patients they were found as unique pathogen.
- If we search, we can also identify mixed bacterial-viral CAP as a common cause of CAP. Adenovirus and Rhinovirus were the most prevalent viral agents in mixed pneumonias.
- Streptococcus pneumoniae, alone or in association with virus, was the most prevalent agent, and one out of two pneumococcal CAP was associated with at least one virus. Viruses can have an important role in pathogenesis of pneumococcal CAP.
- Searching virus should be considered in the study of hospitalized CAP.

P2461
The diagnostic yield of the pneumococcal urinary antigen test in clinical practice and its impact on antibiotic therapy
Wendy Laijen, Dominic Snijders, Wim Boersma. Department of Pulmonary Medicine, Medical Centre Alkmaar, Alkmaar, Netherlands

Background: The pneumococcal urinary antigen test (PUAT) is commonly used for the aetiological diagnose of community-acquired pneumonia (CAP) and can be useful for pathogen-directed therapy. The aim of this study was to evaluate the diagnostic yield of the PUAT and the impact on antibiotic therapy in patients with CAP and a positive PUAT result.

Methods: A retrospective study of adults hospitalised with CAP between 2005 and 2007 was performed. All patients were tested by PUAT. Sensitivity of the PUAT was determined and whether antibiotic treatment was adapted to the PUAT result.

Results: 681 patients with CAP were included. Causative micro-organisms were isolated by using conventional methods in 243 (35.7%) patients. The pathogen most frequently identified was S. pneumoniae in 91 (13.4%) patients, with an increase of diagnostic yield by the PUAT to a total of 178 (26.1%) patients. The PUAT increased the total number of aetiological diagnosis from 35.7% to 48.5%. The PUAT was positive in 37 of 55 patients with definitive pneumococcal pneumonia (67.3%). PUAT was positive in 56 of 95 pneumococcal cases (definite and probable) giving an overall test sensitivity of 59.0%. The test specificity was 93.2%. A positive PUAT led to narrowing antibiotic treatment in 63 (41.2%) patients.

Conclusion: The PUAT is a useful technique for early detection of S. pneumoniae in patients with CAP, but the test is less sensitive in this clinical setting than prospective studies indicate. The PUAT results led the physician to narrow the antibiotic treatment, but insufficient adherence to treatment guidelines of CAP when a PUAT is positive limits its impact.

P2462
Incidence and risk factors of MRSA pneumonia
Katja Verhamme1, Francis Maton1, Krijn Van Varenbergh1,2, Paul Jordens4, 1Department of Infection Control and Epidemiology, OLVZ, Aalst, Belgium; 2MGK. OVZ, Aalst, Belgium; 3Department of Microbiology, OVZ, Aalst, Belgium; 4Department of Respiratory Diseases, OLZ, Aalst, Belgium

Introduction: Data on the incidence of MRSA pneumonia in Europe are scarce. Objective: To study the incidence of MRSA pneumonia and its related mortality. Methods: Data from the OLZ hospital, a 939-bed, university-affiliated teaching hospital in Belgium, were used. The study period ran from 2006 to 2009. All respiratory tract samples, positive for MRSA, were retrospectively collected from the automated microbiology database. As multiple samples per patient were available during follow-up, only the first MRSA respiratory tract sample was considered. Of all patients with MRSA positive respiratory tract samples, the complete medical records, including chest X-ray or chest CT scans were reviewed by a pulmonaryologist. Patients were defined to have pneumonia according to the ECDC criteria. Risk factors such as comorbidity and previous use of antibiotics were studied.

Results: During follow-up, 197 patients with a MRSA positive respiratory tract sample were identified. 46 of these 197 patients developed an MRSA pneumonia of which 30 had a nosocomial pneumonia. The overall incidence of MRSA pneumonia was 0.49/10000 patient days. 25 of the 46 MRSA pneumonia were detected at ICU. In patients with MRSA pneumonia, the mortality was high, 24 of the 46 patients (52%) died during follow-up versus 32% in patients with MRSA colonization of the respiratory tract was 32%. The mean time from admission to MRSA pneumonia was 13.6 days. 50% of patients with MRSA pneumonia were previously (during current hospital admission) treated with an antibiotic vs 32.5% in MRSA colonized patients.

Conclusion: The incidence of MRSA pneumonia is low but mortality in these patients is high. Previous use of antibiotics is one of the main risk factors of an MRSA pneumonia.

P2463
Comparison of community acquired pneumonias which require admission to intensive care unit depending on etiology: Legionella vs pneumococcus
Maria Alfonso1, Marta Inchausti1, Beatriz Gómez1, Nuria Marina1, Luis Alberto Ruiz1, Ainhoa Gómez1, Sandra Pedrero1, Iraite Seijas1, Rafael Zakacain1, 1Pneumology, Cruces Hospital, Barakaldo, Spain; 2Intensive Care Unit, Cruces Hospital, Barakaldo, Spain

Objective: To describe the differences between pneumococcal bacteremic pneumonias (PBP) and Legionella pneumonias (LP) which needed admission to Intensive Care Unit (ICU).

Methods: A cross sectional study was performed from 1/1/2000 to 1/1/2010. We analyzed patients with diagnosis of PBP and LP. All patients were admitted in the ICU of our Hospital. We analyzed clinical, analytical and prognosis differences.

MONDAY, SEPTEMBER 26TH 2011
depending on etiologic agents: Pneumococcus (positive blood culture) and L. gionella (positive urine antigen). Immunodeficient patients and health care patients were excluded.

**Results:** We included 115 patients: 63 (55%) PBP and 52 (45%) LP

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<td>0,0003</td>
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**Conclusions:** 1. Both groups had a similar age. Patients with LP were more smokers and suffered less pleural pain. 2. Patients with LP had more hipoanemia and received previous antibiotic treatment on higher rates. 3. Admission NBI had greater severity indexes with more favourable evolution. 4. Mortality was similar in both groups.

**P2464 Evaluation of the Legionella V-Test compared to the BinaxNOW to detect Legionella serogroup 1 antigen in urine samples**

Evy De Witte, E. De Witte, E. De Witte. 1Vaccin and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; 2Intensive Care Unit, Hospital of Mataro, Fundacio Privada Salut del Consorci Santuarios del Marem, Mataro, Spain

The performance and user friendliness of a new immunochromatographic assay, the Legionella V-Test (Coris Biocomb) for the detection of Legionella pneumophila serogroup 1 antigen in urine (uAg) were evaluated by comparing its results with the BinaxNOW Legionella uAg-test results (Inverness Medical).

For direct uAg testing using both tests, 129 previously collected and frozen urine samples were used: 61 specimens from pneumonia patients during a outbreak: 34 from the 41/129 (32%) samples tested were BinaxNOW positive. The sensitivity and specificity of the V-Test was comparable but the new BinaxNOW was even more user-friendly test.

**Results:**

<table>
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<tr>
<th>Legionella V-Test</th>
<th>BinaxNOW Legionella</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (–)</td>
<td>86</td>
<td>–</td>
</tr>
<tr>
<td>Positive (+)</td>
<td>1</td>
<td>87</td>
</tr>
</tbody>
</table>

**Conclusions:**

1. Both groups had a similar age. Patients with LP were more smokers and suffered less pleural pain. 2. Patients with LP had more hipoanemia and received previous antibiotic treatment on higher rates. 3. Admission NBI had greater severity indexes with more favourable evolution. 4. Mortality was similar in both groups.

**Material and method:** Forty-eight pneumonia cases that were followed up in a tertiary care center between September 2008 - September 2010 and in whom MRSA or MSSA was isolated from initial respiratory specimens were analyzed.

**Findings:** MRSA was isolated in 19 and MSSA in 29 of 48 cases (38 male, mean age 61.5 ±17.9). Risk factors for health-care-associated pneumonia (HCP) (33 vs 16%, p <0.001), history of hospitalization (29 vs 22%, p=0.016), surgical intervention (12 vs 4%, p=0.033) and admission to intensive care unit (14 vs 4%, p=0.014) in the preceding three months were more common in cases with MRSA pneumonia. Length of stay in the intensive care unit (11.5±4.1 vs 2.7±0.8 days, p=0.048) and in the hospital (23.1±4.1 vs 13.9±1.6 days, p=0.049) were longer in cases with MRSA pneumonia. There was no significant difference in mortality between the two groups (31.6 vs 37.9%).

Three MRSA pneumonia cases without risk factors for healthcare-associated pneumonia were diagnosed as community-acquired MRSA (CA-MRSA) pneumonia. The latter cases were found to be older, this difference not reaching statistical significance (76.3±7.2, p=0.093). There was no difference in the other clinical and biochemical parameters.

**Conclusion:** HCAP and CAP caused by S. aureus is associated with significant mortality and morbidity. There are too few cases to better define CA-MRSA pneumonia.

**P2466 A worldwide perspective of nursing home pneumonia beside community acquired pneumonia**

Adamantia Liakopoulou1, Eva Polverino2, Catia Cillozzi2, Paula Peyrani3, Julio Ramirez4, Rosario Menendez4, Antoni Torres5. 1Respiratory and Critical Care Unit, Evangelismos Hospital, Athens, Greece; 2Respiratory Disease Department, Hospital Clinic, Barcelona, Spain; 3Infectious Disease Department, University of Louisville, Louisville, United States

**Background:** Nursing home acquired pneumonia (NHP) is the leading cause of death among long-term care patients and the second most common cause of transfers to hospital. The objective of the study was to characterize the incidence, microbiological, and clinical outcomes of NHP requiring hospitalization in comparison with Community Acquired Pneumonia (CAP) patients.

**Methods:** A secondary analysis of 5,176 patients from the Community Acquired Pneumonia Organization database (CAPO) was performed. World regions were defined as North America (I), Latin America (II), Europe (III), and Asia and Africa (IV).

**Results:** 287 patients (6%) were identified as NHP (mean age 80 yrs). The incidence of NHP was 31, 39, 28, and 1% in the regions I, II, III, IV, respectively. Thirty two patients (11%) required ICU admision. Etiology was defined in 1,403 (27%) of CAP cases instead of 68 (24%) with NHP. The most common isolated pathogens included Streptococcus pneumoniae (34%), Staphylococcus spp (7%) and Haemophilus influenzae (8.5%). Gram(-) pathogens and Staphylococcus spp (29%) were more common in patients with NHP, particularly in North America. The NHP presented more frequently with pleural effusions (28% vs 19%) and multilobar involvement (31% vs. 24%) than CAP patients. Time to clinical stability was 5.9 days in NHP and 4.7 days in CAP patients (p<0.01). The 1-month mortality rate was statistically higher in NHP patients than CAP patients (41% vs. 18%, p<0.01), such as for CAP-related mortality rate (17% vs. 5.4%, p<0.01).

**Conclusions:** NHP patients over the world and can be considered a different clinical entity in terms of presentation, microbiology, clinical course and mortality.

**P2467 Influence of streptococcus pneumoniae serotypes in clinical outcomes of pneumonias**

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In adults, the influence of Streptococcus pneumoniae (Sp) serotypes on pneumonia mortality remains unclear.

**Aim:** To describe the characteristics of adult patients with pneumonia caused by Sp isolated in invasive strains and the influence of different serotypes in clinical outcomes.

**Method:** A retrospective study of Sp serotypes in invasive strains isolated from patients with pneumonia, describing the clinical features and complications. Blood and pleural fluid samples were processed using the BacT-Aert-Mbl system. All strains were sent to the Reference Laboratory for serotyping. Serotypes were divided into 3 groups [1]: High invasive disease potential (H group): 1, 5 and 7 F; Low invasive potential (L group): 3, 6A, 6B, 8, 19F and 23F; the rest were named as other serotypes (O group).

**Results:** Between January 2009 and December 2010 were isolated 53 Sp strains, 44 blood samples and 9 pleural fluid (3 patients had both). 18 of them were serotypes of H group, 10 were of L group, and 23 were of O group. There were a total of 50 patients (58% men). Mean age was 56±19. The table shows clinical outcomes.

**Conclusions:** Contrary to what could be expected the pneumonias caused by Sp serotypes of H group had a lower mortality ratio.1 Brueggerman AB et al. Clonal relationships between Invasive and carriage S pneumoniae and serotype- and clone-specific differences in invasive disease potential.
P2468

Pneumococcal pneumonia – Are the new severity scores more accurate in predicting adverse outcomes?
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Background: The severity scores are validated prognostic tools for community-acquired pneumonia mortality and treatment site decision.

Aim: To compare the discriminatory power (DP) of 4 scores – the classic PSI and CURB65 and the most recent SCAP (Yandiola et al. Chest 2009;135:1572-1579) and SMART-COP (Charles et al. Clinical Infectious Diseases 2008;47:375-84) – in predicting major adverse events: death, ICU admission, need for invasive mechanical ventilation or vasopressor support.

Methods: A 5-year retrospective study of patients admitted for pneumococcal pneumonia (PP). The patients were stratified based on admission data and assigned to risk classes (low-medium-high) for each score, as validated by previous studies. Statistical analysis was done based on sensitivity, specificity and area under the curve (AUC) under the ROC curve.

Results: We assessed 142 episodes of hospitalization for PP. We observed 2 deaths, 22 admissions to the ICU, 10 patients needed mechanical ventilation and vasopressor support. The AUC for each score/event is summarized on the following table.

<table>
<thead>
<tr>
<th>Score</th>
<th>Mortality</th>
<th>ICU admission</th>
<th>Mechanical ventilation</th>
<th>Vasopressor support</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI</td>
<td>0.96 ±(0.02)</td>
<td>0.62 ±(0.07)</td>
<td>0.62 ±(0.09)</td>
<td>0.59 ±(0.03)</td>
</tr>
<tr>
<td>CURB65</td>
<td>0.96 ±(0.02)</td>
<td>0.70 ±(0.07)</td>
<td>0.66 ±(0.09)</td>
<td>0.72 ±(0.02)</td>
</tr>
<tr>
<td>SCAP</td>
<td>0.85 ±(0.03)</td>
<td>0.85 ±(0.049)</td>
<td>0.86 ±(0.001)</td>
<td>0.83 ±(0.001)</td>
</tr>
<tr>
<td>SMART-COP</td>
<td>0.88 ±(0.07)</td>
<td>0.85 ±(0.055)</td>
<td>0.81 ±(0.081)</td>
<td>0.82 ±(0.001)</td>
</tr>
</tbody>
</table>

Conclusions: The rate of all adverse outcomes increased directly with increasing risk class in all scores. The new gravity scores (particularly the SCAP score) appear to have a higher DP to all adverse events in our study.

P2469

Clostridium difficile infection following community-acquired pneumonia
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Edinburgh, United Kingdom

Introduction: In this prospective observational study of hospitalized community-acquired pneumonia (CAP) patients, we determined the incidence Clostridium difficile infection (CDI) and its contribution towards treatment failure.

Methods: Data were recorded for 1833 consecutive CAP patients. All patients with 2 or more loose stools during these admissions, had samples sent for Clostridium difficile toxin testing. The association of specific risk factors and development of CDI was assessed by multivariable logistic regression (MVR).

Results: There were 51 cases of CDI following CAP (2.7% of CAP cases). The most frequent antibiotic regimes implicated were amoxicillin/clavulanic acid +/− macrolide (54.9%) or regimes containing cephalosporins (35.3%). 37.3% of CDI cases received more than 2 antibiotics (excluding those used to treat CDI), while only 3 patients were on monotherapy. Mortality secondary to CDI was 21.6% as inpatient, rising to 43.1% at 1 year (compared to 1 year mortality for all CAP patients of 21.3%, p=0.0001). Overall mortality rate for CAP patients was 9% at 30 days.

In MVR analysis, the factors associated with development of CDI were age (AOR 1.04 95% CI 1.01-1.08, p=0.03), duration of admission (AOR 1.06 95% CI 1.04-1.09, p<0.0001), total number of antibiotics during admission (AOR 2.59 95% CI 1.22-5.51, p=0.01), and total duration of antibiotic therapy (AOR 1.14 95% CI 1.02-1.27, p=0.02).

Conclusion: CDI is a relatively uncommon complication of CAP, occurring predominantly in elderly patients. Post CAP, it is, however, associated with increased in-hospital and 1 year mortality. Reducing total antibiotic exposure and duration of treatment might be as important as changing antibiotic class in reducing CDI rates.

P2470

Potential value of an ELISPOT interferon gamma release assay as a diagnostic tool in Q fever infections
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Rationale: Q fever is an emerging zoonosis in the Netherlands, atypical pneumonia being the most common clinical manifestation. Acute disease is followed by resolution in the majority of cases, 10-20% will exhibit the post-Q fever fatigue syndrome (QFS) and 1-5% of patients progresses to chronic disease. Current tests measuring humoral immune response to Coxiella burnetii have considerable limitations in diagnosing these different outcomes. We conducted an exploratory study to determine T cell response to C. burnetii specific antigens using an ELISPOT interferon gamma release assay (Coxiella ELISPOTs).

Methods: An in-house developed Coxiella ELISPOT interferon gamma release assay, using both phase I and phase II antigens was performed on blood samples of 47 Q fever patients.

Results: Coxiella ELISPOT was performed for 7 patients reconvalesced after acute Q fever and 2 chronic Q fever patients (n=1 newly diagnosed, n=1 after completion of treatment). Mean (± SD) spot count for reconvalesced patients was 11±5 (range 1-42) for phase I and 31±15 (range 1-120) for phase II. One patient was diagnosed with QFS and had the highest spot count in both phase I (42 spots) and phase II (120 spots). The newly diagnosed chronic Q fever patient (male, 64 years) showed a predominant responsiveness to phase I antigen (spot count Phase I 209, Phase II 177). The other chronic Q fever patient (male, 67 yrs) had finished a 18 month antibiotic treatment for Q fever endocarditis. Coxiella ELISPOT showed a marked T cell unresponsiveness to both phase I (3 spots) and phase II antigens (0 spots).

Conclusion: Different clinical Q fever outcomes are associated with marked differences in Coxiella ELISPOT results.
Characteristics and predictors of mortality in patients with pleural infection
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²Respiratory Department, Wansbeck Hospital, Ashington, Northumberland, United Kingdom

Background: Pleural infection is increasing in incidence and causes significant morbidity and mortality. Many UK patients are cared for by non-respiratory teams.

Aims of study: To evaluate recovering of autonomic cardiac control in patients with community-acquired pneumonia.

Methods: A 12 months prospective multicenter and longitudinal study was performed in several hospitals of a Spanish mediterranean area (Comunidad Valenciana). We included patients over 65 with CAP diagnosis. We analyzed mortality related factors (comorbidities, clinical, radiological and laboratory findings, complications) and mortality risk related to PSI or CURB65 scores. Statistical analysis included Chi Square with significance p<0.05.

Results: 750 patients were included, with mean age of 76.7±7.5 years. 63.9% were men. 5.1% died. In our cohort, mortality rate attending PSI score or CURB65 was consistent as reported series (Table 1). However, CURB65 accuracy to predict mortality has not been validated in elderly population.

Aim: To analyze the predictive mortality value of CURB65 scale versus PSI score in patients with CAP older than 65 years old.

To characterise patients with pleural infection, assess standards of care and identify clinical variables predictive of outcome.

Results: 45 cases were included, 69% male, median age (IQR) 72 (46-78) years. 36% had a recent pleural procedure prior to developing infection. 36% were immunosuppressed, 13% had an underlying malignancy. 73% were under respiratory care. Inpatient mortality was 20%. Outcomes varied between respiratory and non-respiratory care: Mortality: 9% v 50% OR (95% CI) 0.10 (0.019-0.51) p=0.006. Drain-related complications: 27% v 58% OR (0.06-1.06) p=0.056. Length of stay: mean (SD) 18.3 (20.1) v 35.3 (28.8) days HR 4.16 (1.59-10.9) p=0.0035. In univariate analysis mortality was associated with increased age, high urea, low serum albumin and low pleural fluid protein level. On multivariate analysis mortality was predicted by age≥75 years OR 10.7 (1.75-66.6) p=0.010, albumin <30mg/dl OR 6.41 (1.47-35.7) p=0.032, and non-respiratory care OR 6.7 (1.07-42.4) p=0.041.

Conclusions: Pleural infections are often iatrogenic and associated with malignancy or immunosuppression. Complications with chest drains are common. Mortality is highest in older patients with low albumin. Patients under respiratory care have better outcomes.

The three patients had a very similar clinical picture: poor social background (disorganized families, homeless, prisoners), history of intravenous drug use (especially heroin), recently using etnobotanic powders intravenously, positive HCV, negative HIV and VHB, multiple bilateral lung opacities on X-Ray, similar symptomatology (fever, dyspnea, cough with macropurulent sputum), tricuspid valve endocarditis (confirmed by echocardiography). The bacteriological exam (bacteriemias and sputum) were negative probably related to the empirical antibiostatic usage prior hospitalisation. Two patients improved slowly with antibiostatic treatment. One critically ill patient died with septic shock and multiple organ insufficiency.

Conclusions: The increased number of cases with multicentric pneumonia and endocarditis related to the usage of the ethnobotanic drugs of legal status reveal the harmful effect when used intravenously.

Table 1

<table>
<thead>
<tr>
<th>Cohort patients (%)</th>
<th>PSI (%)</th>
<th>Cohort patients (%)</th>
<th>CURB65 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>0.6</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>1.2</td>
<td>0.9-2.8</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>6.5</td>
<td>8.2-9.3</td>
<td>4</td>
</tr>
<tr>
<td>V</td>
<td>16.8</td>
<td>27-29.2</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>CURB65</th>
<th>PSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (1-3)</td>
<td>%</td>
</tr>
<tr>
<td>Moderate risk (4)</td>
<td>%</td>
</tr>
<tr>
<td>Severe risk (5)</td>
<td>%</td>
</tr>
<tr>
<td>Low risk (0-1)</td>
<td>85.3</td>
</tr>
<tr>
<td>Moderate risk (2)</td>
<td>14.7</td>
</tr>
<tr>
<td>Severe risk (3-5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: Although mortality rate in our cohort is closed to reported data, CURB65 in elderly patients with CAP underestimate the severity of CAP compared to PSI scores.

271. Assessment of severity and predictors of outcomes in community-acquired pneumonia

P2475

Slow recovering of altered autonomic cardiac control in patients with community acquired pneumonia
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Altered autonomic cardiac control is associated with severe arrhythmias, heart insufficiency and sudden death.

Aim: To evaluate recovering of autonomic cardiac control in patients with community acquired pneumonia (CAP). 73 patients with nonsevere CAP (nCAP) and 14 patients with severe CAP (sCAP) were studied at the day of hospital admission and in follow-up periods of 3 and 14-16 days after admission. Controls (CG) included 48 healthy subjects. Autonomic cardiac control was estimated via analysis of fluctuations of consecutive RR intervals at 10 min ECG record. Heart rate variability (HRV) indexes included standard deviation SDNN, coefficient of variation CVNN, 0.04-0.15 Hz and 0.15-0.4 Hz bands spectral power. At admission HRV indexes were significantly lower in both CAP groups than in CG. All patients showed clinical and functional recovery. nCAP HRV indexes reached CG values on the 15th day after admission. sCAP HRV indexes remained lower than in nCAP and CG.

Conclusions: Autonomic cardiac control is significantly altered in patients with CAP. Predicted recovery period may take up to 6 months in patients with severe CAP and extreme physical workload should be limited due to increased cardiovascular risk.
In pneumonia, pathogen-host interaction may evoke pulmonary endothelial permeability despite efficient antimicrobial therapy, resulting in life-threatening lung failure. Angiopoietin (Ang)-1 mediated Tie-2 activation reduces and Ang-2 expression was increased. Further, we detected reduced pulmonary mRNA expression of Ang-1 and Tie-2 and increased Ang-2 expression in murine lung tissue following infection with *S. pneumoniae*. These results suggest a central role of the Ang-1/Tie-2-system in pneumonia-evoked inflammation and permeability, and provide a new therapeutic perspective for severe pneumonia.

**P2478**
Differences between local and systemic inflammatory response in patients with community acquired pneumonia (CAP) 
Leanza Calisi,1,2 Monica Morlacchi,1,2 Letizia Corinna Morlacchi,1,2 Stefano Aliberti,3 Sonia Seghezzi,1 Valeria Giunta,1 Marta Di Pasquale,1 Giulia Spoletini,1 Anna Maria Brambilla,3 Jose Bordon,4 Fabio Giuliani,1 Samantha Galbiati,1 Barbara Dallari,1 Andrea Gramegna,1 Letizia Corinna Morlacchi,1,2 Stefano Aliberti,2,3 Sonia Seghezzi,1 Valeria Giunta,1 Marta Di Pasquale,1 Giulia Spoletini,1 Anna Maria Brambilla,3 Jose Bordon,4 Fabio Giuliani,1 Samantha Galbiati,1 Barbara Dallari,1 Andrea Gramegna,1 Letizia Corinna Morlacchi,1,2 Stefano Aliberti,2,3 Sonia Seghezzi,1 Valeria Giunta,1 Marta Di Pasquale,1 Giulia Spoletini,1 Anna Maria Brambilla,3 Jose Bordon,4 Fabio Giuliani,1 Samantha Galbiati,1 Barbara Dallari,1 Andrea Gramegna,1

Understanding inflammatory response is a crucial issue in the management of CAP. The aim of our study was to evaluate both local (lung) and systemic (serum) inflammation on admission in hospitalized patients with CAP. An observational prospective study was performed on consecutive patients hospitalized for CAP from April to December 2010 at the Respiratory Dept., Poliomicological Hospital, Milan, Italy. Within 24 hours after admission, specimens of blood and exhaled breath condensate (EBC) were collected. The following cytokines were detected: IL-1α, IL-1β, IL-2, IL-6, IL-10, TNF-γ and INF-γ and anti-inflammatory (IL-4 and IL-10). A total of 43 subjects were prospectively enrolled (26 males; mean±SD age: 71±18 yrs). Local and systemic inflammatory patterns on admission are shown in Table (Mean ± SD).

<table>
<thead>
<tr>
<th>Cytokine, pg/mL</th>
<th>EBC</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0.46±0.48</td>
<td>1.28±0.90</td>
</tr>
<tr>
<td>IL-4</td>
<td>1.69±0.71</td>
<td>1.43±0.64</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.01±0.02</td>
<td>108.33±150.03</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.34±0.04</td>
<td>128.80±340.03</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.20±0.16</td>
<td>1.49±1.50</td>
</tr>
<tr>
<td>INF-γ</td>
<td>0.02±0.07</td>
<td>12.79±38.16</td>
</tr>
<tr>
<td>TNF-γ</td>
<td>0.10±0.29</td>
<td>13.30±28.62</td>
</tr>
<tr>
<td>IL-1α</td>
<td>0.07±0.13</td>
<td>0.75±1.23</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.21±0.33</td>
<td>1.20±0.85</td>
</tr>
</tbody>
</table>

Pro-inflammatory interleukins were increased in patients undergoing mechanical ventilation on admission in comparison to the rest of the population in both serum (IL-1α 0.57±1.02 vs. 0.11±0.12, respectively; p<0.007) and EBC (IL-6 0.31±0.28 vs. 0.08±0.06, respectively; p=0.001). These findings may help to understand the decompartmentalization of the inflammatory response, which takes place since the very early stages of the infection in hospitalized patients with CAP.

**P2479**
Validity of CRB-65 in LRTI in primary care: A prospective study in 12 European countries 
Samuel Coenen1,2, Theo Verheij1, Greet Ieven2, Christine Lammens2, Christopher Butler3, Paul Little3, Henrik Große3,1

Background: CRB-65, a useful tool to predict community-acquired pneumonia (CAP) outcome in hospitals, has been recommended for use in primary care. CRB-65 scores are calculated by assigning one point for each of: the presence of Confusion, Respiratory rate ≥ 30 per minute, Blood pressure systolic < 90 mm Hg or diastolic ≤ 60 mm Hg, and age ≥ 65 years. Aim: To assess the validity of CRB-65 to predict poor prognosis in adults presenting to primary care with lower respiratory tract infection (LRTI). Methods: Clinicians prospectively recorded clinical features on a case registration form. Patients had a chest X-ray within 7 days after inclusion. A notes review was performed. We used a two-level logistic regression model (with patients nested within clinicians) to assess the association between a CRB-65 score ≥ 1 and mortality and a combination of re-consultation and hospital admission, and tested for interaction to assess differences in these outcome between patients with and without CAP. Results: None of the 3112 included patients died due to the LRTI. Complete data were available in 2627 (84%) patients. Of these, 866 (33%) had a CRB-65 score ≥ 1, 108 (4%) had CAP, and 488 (19%) re-consulted or were admitted to hospital. Both a CRB-65 score ≥ 1 and CAP were associated with more re-consultations or hospital admission (odds ratio (95%CI): 1.32 (1.06–1.64) and 2.18 (1.13–4.21), respectively). The interaction term was not significant (1.17 (0.57–2.41)). Conclusion: In patients presenting to primary care with LRTI, low mortality and low prevalence of CAP limit the usefulness of CRB-65. Nevertheless, a CRB-65 score ≥ 1 is associated with a significant increase in re-consultations and hospital admissions.

**P2480**
Vascular events following hospitalisation for community acquired pneumonia Ahan R. Akram1,2, James D. Chalmers1, Aran Singanayagam3, Gillian B. Fleming4, Joanne K. Taylor5, Duncan Mills6, Adam T. Hill1,1 Department of Respiratory Medicine, New Royal Infirmary of Edinburgh, Edinburgh, United Kingdom;2 College of Medicine, University of Edinburgh, Edinburgh, United Kingdom

Objective: To determine if patients with community acquired pneumonia (CAP) are at increased risk of vascular events following discharge. Methods: Patients enrolled in a prospective study for CAP who survived to hospital discharge were followed up at 1 year. A cohort matched to age, sex, co-morbidities and vascular risk factors were included and the incidence of vascular events and mortality were recorded. Results: 1321 patients were included (50.3% male, median age 65 (IQR 48–77), 23.7% had a prior history cardiovascular events) with 1321 matched controls. 12.3% of CAP patients died after discharge by 1 year, with 28.9% attributed to cardiovascular events or stroke. The incidence increased with age. 156 patients required hospitalisation within 1 year for one or more vascular event; myocardial infarction (MI) n=74, cardiac failure n=61, for cardiac arrhythmia n=31 and stroke n=12. Of the 74 patients with MI, there was a significantly increased incidence when compared to the control group (fig1).
Using multivariate logistic regression analysis, major predictors of cardiovascular deaths following CAP were age (OR 1.04 95% CI (1.02-1.07), p<0.0001), prior history of cardiovascular events (2.70 (1.47-4.96), p<0.001), ICU admission during hospital admission (1.87 (1.04;3.38), p=0.04) and anaemia (0.98 (0.97-0.99), p=0.0007).

Conclusion: Hospitalisation for CAP is associated with an increased risk of cardiovascular events and mortality at 1 year.

P2483
Severe complicated pneumococcal pneumonia in young adults
Sebastian Ellis, Matthew Harris, Suzanne Shuttlesworth, Chris Taylor, Aye Aye Lwin. Respiratory, Southampton General Hospital, Southampton, Hampshire, United Kingdom

Background: Pneumococcal pneumonia causes parapneumonic effusion (PE) in 40%-57%. Severity can be influenced by both host characteristics e.g. co-morbidity, age and vaccination status and, bacterial factors.

Aims and objectives: To study the relationship between host characteristics (age, co-morbidity and previous vaccination) and disease severity in adults admitted with pneumococcal pneumonia.

Methods: A cohort of 21 inpatients with pneumococcal pneumonia between December 2010 to January 2011 were retrospectively studied using electronic patient records, medical notes and the PACS system. Uncomplicated PE (UPPE) was defined as pleural fluid pH >7.2, complicated PE (CPPE) as pH <7.2 and empyema as visible purulent fluid.

Results: 21 patients were admitted with pneumococcal pneumonia, 8 male and 13 female, median age 48 years (range 18-76). 9 (43%) had no associated co-morbidity, of which 7 were <65 years. 6/9 developed pleural effusion (1 UPPE, 4 CPPE and 1 empyema), 4 (72%) required chest drainage, none of these 4 were vaccinated. All patients who developed pleural effusion or empyema, 9/21 (38%), had an admission CRP > 100 (range 101-500) and albumin <35 (range 16-32). 7/21 (33%) patients were admitted to the intensive care unit (ICU). 47% had no associated co-morbidities, median age was 33 (range 29-48) and all 4 patients were not vaccinated.

Conclusion: Our study highlights that along with high risk groups, young un-vaccinated adults with no co-morbidity are also at risk of developing severe pneumococcal pneumonia with complicating pleural effusion or empyema.

P2484
Impact of pneumococcal urinary antigen testing in the clinical presentation and outcome of pneumococcal bacteraemic community acquired pneumonia
Luis Alberto Ruiz, Maria Alfonso, Ainhoa Gomez, Sandra Pedrero, Nuria Marina, Marta Inchausti, Inxute Seijas, Carmen Jaca, Rafael Zalacaín. Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain Pneumology, Cruces Hospital, Barakaldo, Spain

Aim: To describe the clinical characteristics and outcome of a group of patients diagnosed with pneumococcal bacteraemia community acquired pneumonia (PB-CA) depending on the results of pneumococcal urinary antigen testing (PUAT).

Methods: We have studied all patients admitted to the Respiratory Service and/or ICU of our hospital for 10 years. Patients have been divided into two groups according to the results of PUAT (BINA®). Exclusion criteria included (1) lack of antibody immunity deficiency syndrome, other immunodeficiencies or under immunosuppressive treatment; (2) health care associated pneumonia.

Results: We have studied 250 patients, 233 out of them underwent UPATD.

Conclusions: 1. PUAT positivity was associated with an early antibiotic prescription at the emergency department at admission. 2. Patients with positive PUAT were more frequently admitted to ICU. They also had a higher mean hospital stay but there were no significant differences regarding severity according to PSI and CURB score. 3. Patients under negative PUAT had a lower but no significant mortality rate.

P2485
Is pneumonia in elderly an enigma: A study from a multispeciality hospital in rural India
B N B Mahaveera Prasad, C A Tukaram. Medicine, Military Hospital Wellington, Wellington Barracks, The Nilgiris District, Tamilnadu, India

Aim: To study the manifestations and outcome of pneumonia in elderly from a multispeciality hospital in rural India.

Conclusions: 1. PUAT positivity was associated with an early antibiotic prescription at the emergency department at admission. 2. Patients with positive PUAT were more frequently admitted to ICU. They also had a higher mean hospital stay but there were no significant differences regarding severity according to PSI and CURB score. 3. Patients under negative PUAT had a lower but no significant mortality rate.
P2486 Prospective comparison between chest ultrasound and X-ray in two planes in patients with suspected community-acquired pneumonia. Intermediate results (02/2011) of a prospective multicenter DEGUM-/ÖGUM-study

Aim: The aim of the prospective study is to define the sensitivity of chest ultrasound (US) in diagnosing and follow-up of community-acquired pneumonia (CAP).

Patients and methods: US was performed in 326 patients (age 18-95 years; 211 males, 115 females) with suspected CAP. The results were first compared to X-ray in two planes. In case of positive US and negative or inconclusive X-ray a low-dose computed tomography (CT) was performed. Sonographic characterisation of pneumonia was carried out at day 0, between day 5-8 and between day 13-16.

Results*: US / X-ray / CT / Number of patients:

- negative / negative / not done / n=109
- positive / negative / positive / not done / n=153
- positive / positive / negative / not done / n=41
- positive / negative / negative / not done / n=22
- negative / negative / negative / not done / n=13
- negative / inconclusive / positive / not done / n=2
- US was inconclusive in 5 patients, which had to be deleted according to the study protocol.

Conclusions: The intermediate results suggest a high sensitivity and specificity of US in diagnosing and follow-up CAP. The final results will be available in September 2011.

P2487 Does a clinical score helps in the management of hospital-acquired pneumonia in nonventilated patients?

Bertrand Heres, Zhineh Gazaee. Service de Pneumologie, Centre de Forcilles, Fénolles Attilly, France

Hospital-acquired pneumonia (HAP) is increasingly frequent in nonventilated (NV) patients. Because of the difficulty of obtaining invasive diagnostic procedures outside an intensive care unit (ICU), a clinical score could be useful for the management of NV patients. We tested the diagnostic accuracy of a score (SCOPNOFOR) suitable for NV patients with clinical suspicion of HAP, obtained by combining the following clinical parameters (minimal value = 0, maximal value = 9): non cancerous comorbid condition (0=nosent, 1=present); solid cancer (0=absent, 1=present); pulmonary comorbidity (0=nosent, 1=pseudopneumothorax, 2=pseudocyst); previous antibiotics (0=yes, 1=no); radiographic infiltrate (0=no or diffuse, 2=localized); NV ICU (0) or ward (1) patient. The score was calculated before a protected specimen brush was obtained by bronchoscopy in all cases and its value was compared with bacteriological results to assess sensitivity (Se) and specificity (Sp).

HAP was confirmed in 45 (54.6%) of 84 suspected episodes disclosing in major part nonfermenting (35.6%) and enteric (42.2%) gram-negative bacilli, staphylococci (26.7%) and streptococci (26.7%) spp. Polymericbacterial HAP was present in 37.8% of episodes. The mean ± SD SCOPNOFOR value was 5.3±1.6 and 4.3±1.5, respectively, for the 45 HAP episodes and the 39 non HAP episodes (p=0.003). Se and Sp were respectively at a SCOPNOFOR value more than 5, 53% and 79%, and more than 2, 27% and 95%. We conclude that SCOPNOFOR can at least 50% in 75% of patients with defined HAP according to the chosen cut-off. These data support the need for establishing an etiologic diagnosis in suspected HAP in NV patients.

P2488 Comparison of four systems for assessing severity of community acquired pneumonia

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Introduction: The use of severity scores for community acquired pneumonia (CAP) is recommended by many clinical guidelines. However, debate about the preferred system is ongoing.

Objective: To compare the performance of 4 systems to identify severe CAP.

Material and methods: We reviewed 176 patients diagnosed with CAP, admitted in a Pneumology ward, from January 2007 to July 2009. We compared 4 systems: Pneumonia Severity Index (PSI), CURB65, modified American Thoracic Society criteria for severe pneumonia (AtSrn) and SCAPE score.

We divided the patients in 2 groups: low-risk and high-risk, the later defined as CURB65 ≥3, PSI classes IV, AtSrn ≥1 major criteria or ≥3 minor criteria and SCAP score ≥3 major criteria or ≥3 minor criteria. We evaluated the performance of all four systems in low and high-risk patient adverse outcomes, defined as mortality and need for ICU admission, based on sensitivity, specificity and area under the ROC curve (AUC).

Results: Sensitivity and specificity (95% confidence interval in brackets) were, respectively: CURB65 27.33% [9.7 - 56.6] and 91.5% [86.3 - 94.9]. PSI 81.8% [52.3 - 94.9] and 55.8% [48.1 - 63.1]. AtSrn 54.6% [28.0 - 78.7] and 95.8% [91.5 - 97.9]. SCAPE 81.8% [52.3 - 94.9] and 70.9% [63.6 - 73.1].

AUC was: CURB65 0.594, PSI 0.688, AtSrn 0.752 and SCAPE 0.764.

Conclusions: PSI and SCAPE were the most sensitive systems, while CURB65 and AtSrn were the most specific. Although the most discriminative capacity was found in SCAPE, it presented many false positives. Probably, a good approach would be to rely on clinical judgment, triage of high risk patients with PSI or SCAPE and use of AtSrn to determine need for ICU admission.

P2489 Value of serum procalcitonin levels in the differential diagnosis of pneumonia and pulmonary embolism

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Objective: Procalcitonin (PCT), a precursor hormone of calcitonin is secreted from the thyroid. It was increased in blood in bacterial infections. The aim of the study was to determine the serum procalcitonin levels in differentiating community-acquired pneumonia (CAP) from pulmonary embolism (PE).

Methods and patients: Fifty-eight patients with 1≥1 of the following symptoms; fever, cough, dyspnoea, haemoptysis, sputum, chest pain; and PE were included in the study. Thirty patients were diagnosed as CAP and 27 patients as PE. One patient with suspected PE was excluded because of negative pulmonary CT angiography. Serum PCT values of all patients were measured and recorded before treatment was started.

Results: Median values of PCT were in patients with PE 0.05 ng/ml in patients with CAP 1.38 ng/ml. The area under ROC curve was 0.83. With an optimal cut-off value 0.27 ng/ml for differentiating PE and CAP, sensitivity was 76.4%, specificity 85.2%, negative predictive value 76.7%, positive predictive value 85.2%, and accuracy 80.7%.

Conclusion: Serum PCT has a high diagnostic value in the differential diagnosis of PE and CAP. Serum PCT can be used in differentiating CAP and PE as an inflammatory marker.

P2490 The value of exhaled breath condensate “pH” to evaluate the severity of disease and the response to treatment in patients with community acquired pneumonia

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Introduction: There is no practical procedure in defining severity of community acquired pneumonia (CAP) and evaluation of response to treatment. Recently “exhaled breath condensate pH” measurement as a noninvasive, reproducible and easily performed method is in use to diagnose some airway and pulmonary diseases. We planned this study to measure the severity and response to treatment in patients with community acquired pneumonia by using this method.
P2491
Cost and outcomes of pneumococcal community-acquired pneumonia among adults in the United Kingdom
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Background: Community-acquired pneumonia (CAP) is associated with substantial morbidity and mortality among adults in the United Kingdom (UK). S. pneumoniae is the most common cause of CAP.

Aims and objectives: The study objective was to evaluate the clinical and economic burden of pneumococcal CAP among adults in the UK.

Methods: A cost-outcomes model was developed to estimate the inpatient costs and health outcomes associated with pneumococcal CAP among adults above 50 years old in the UK. Health outcomes were measured in terms of life-year (LY) and quality-adjusted life year (QALY) lost. National data sources were used to estimate hospital admissions, deaths and costs with CAP as primary diagnosis for 2009/10. Since specific pathogens for pneumonia are not commonly identified, the proportion of CAP attributable to S. pneumoniae was estimated based on literature findings. A structured literature search was conducted to identify UK specific quality of life data.

Results: We estimated that there were 58,604 annual hospital admissions for pneumococcal CAP for adults above 50 years old in the UK, costing more than £122 million per year. In addition, there were 13,161 deaths per year resulting in 87,533 pneumoniae CAP for adults above 50 years old in the UK. Health outcomes were measured in terms of life-year (LY) and quality-adjusted life year (QALY) lost. National data sources were used to estimate hospital admissions, deaths and costs with CAP as primary diagnosis for 2009/10. Since specific pathogens for pneumonia are not commonly identified, the proportion of CAP attributable to S. pneumoniae was estimated based on literature findings. A structured literature search was conducted to identify UK specific quality of life data.

Conclusion: We estimated that there were 58,604 annual hospital admissions for pneumococcal CAP for adults above 50 years old in the UK, costing more than £122 million per year. In addition, there were 13,161 deaths per year resulting in 87,533

P2492
Relationship between the presence of hypoxemia and the inflammatory response measured by C-reactive protein in bacteremic pneumococcal pneumonia
Francisco Sanz1, Concepción Gimeno 2, Tomás Lloret1, Nuria Torroja1, Marisa Britos1, Estrella Fernández1, Angela Cervera1, Maria Carmen Aguilar1, Eusebi Chiner6, José Blanquer 7.

Aims: To evaluate whether the presence of hypoxemia could influence the systemic inflammatory response (C-reactive protein, CRP) in bacteremic pneumococcal pneumonia (Pu-CAP).

Material and methods: We analyzed the relationship between the presence of hypoxemia (PaO₂/FiO₂ < 300) and other clinical parameters and systemic inflammatory response measured by PCR in a series of bacteremic pneumococcal pneumonia. We performed a multiple linear regression analysis considering CRP levels as a dependent variable and other physiological parameters and comorbidities as independent variables.

Results: We analyzed 297 cases of bacteremic pneumococcal pneumonia. The mean PAO2/FIO2 was 277.7 (IQR: 233.3-323.8), and 44.8% (133) showed PaO₂/FiO₂<300. CRP mean was 27.6 mg/dl (IQR: 15.7-39.2). Linear regression analysis showed that pneumonia severity (PSI score) (regression coefficient: -0.21, p = 0.047) and the presence of some immunosuppressant factor (regression coefficient: -0.29, p = 0.002) were independently associated with CRP levels. The model showed a correlation of 0.333 with r² of 0.125.

Conclusions: In our series, we observed that the degree of hypoxemia, the severity of pneumonia and the presence of some immunosuppressant factors correlates with the systemic inflammatory response measured by CRP in bacteremic pneumococcal pneumonia.

P2493
Usefulness of serum cortisol in assessment for the severity of community-acquired pneumonia
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Background: High cortisol levels are frequently observed in patients with severe infections and are of prognostic value in sepsis. The aim of this study was to evaluate the clinical usefulness of serum cortisol in assessment for the severity of community-acquired pneumonia (CAP).

Materials and methods: This study analyzed the results of 52 CAP subjects admitted in Changwon Fatima Hospital between July 2008 to May 2010. Total serum cortisol, infection markers such as C-reactive protein (CRP), procalcitonin (PCT) and CURB (Confusion, Uremia, Respiratory, Blood pressure)-65 were examined retrospectively.

Results: In clinically unstable subjects on admission day 4, baseline serum cortisol, CURB-65, and CRP were elevated significantly compared to those of stable subjects.

Laboratory parameters and severity scores of the patients according to outcome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinically unstable on day 4 (n=17)</th>
<th>Clinically stable on day 4 (n=35)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/dl</td>
<td>19.9±9.1</td>
<td>8.4±5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>PCT, μg/ml</td>
<td>18.4±8.2</td>
<td>4.2±1.9</td>
<td>0.006</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>43.1±17.6</td>
<td>16.7±1.4</td>
<td>0.037</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>19.9±9.1</td>
<td>8.4±5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>PCT, μg/ml</td>
<td>18.4±8.2</td>
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<td>0.006</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>43.1±17.6</td>
<td>16.7±1.4</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Conclusion: These findings suggest that measurement of serum cortisol in early stage may provide helpful information in the assessment of CAP severity.
Results: The mortality rate was 12.3%. 120 (48%) patients were admitted to the hospital, despite the fact they were classified as risk class I or II. According to guidelines as far as the initial antimicrobial regimen is concerned was poor (152 patients, 60%). A trend towards shorter length of hospitalization was observed in patients treated with an initial antimicrobial in accordance to guidelines compared to those receiving initial regimen in discordance to guidelines.

Conclusion: The implementation of CAP guidelines by chest physicians in the major Greek hospital for thoracic diseases is poor. Improvement of adherence may shorten the length of hospitalization and reduce the financial burden for the national health system.

P2495
Ventilator-associated pneumonia in surgical intensive care unit: Risk factors for mortality and survival period
Hisashi Shoji, Takahiro Takuma, Koichiro Yoshida, Yoshihito Niki. Department of Clinical Infectious Diseases, Showa University, School of Medicine, Tokyo, Japan.

Objectives: The aim of this study was to reveal the prognostic factors of Ventilator-Associated Pneumonia (VAP) in the surgical ICU of Showa University Hospital in Tokyo.

Patients and methods: We reviewed 1629 cases administrated mechanical ventilation in surgical ICU from Apr,2006 to Dec, 2010. In these 1629 cases, 46 patients were diagnosed VAP. We evaluated whether backgrounds, general conditions, laboratory data, chest radiographic features at the time of VAP onset and severity of VAP may contribute to the mortality or survival period.

Results: Twenty-three patients (50%) were dead. Multivariate analyses using significant (p<0.05) parameter in univariate analyses revealed different results, but bilateral pneumonia had significant differences in the both multivariate analyses of mortality and survival period (Table 1 & 2).

Table 1. Multivariate analysis of mortality in patients with VAP

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBROAD*</td>
<td>10.70 (1.0001 to 106.30)</td>
</tr>
<tr>
<td>Re-Operation</td>
<td>36.04 (2.0028 to 630.67)</td>
</tr>
<tr>
<td>Bilateral pneumonia</td>
<td>15.45 (0.0178 to 1360.70)</td>
</tr>
</tbody>
</table>

* IBROAD is a severity index in Japanese Respiratory Society Guidelines. IBROAD in hospital 1, IBROAD in hospital 2, IBROAD in infection, IBROAD in non-infection. More than three parameter is serious.

Table 2. Multivariate analysis survival from Cox proportional hazard model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE</td>
<td>1.008 (0.0245 to 47.00)</td>
</tr>
<tr>
<td>Bilateral pneumonia</td>
<td>2.040 (0.0052 to 0.0562)</td>
</tr>
</tbody>
</table>

Figure 1 shows Kaplan-Meier curves of radiographic findings and survival period.

P2497
Late-breaking abstract: Relationship of asthma to outcome in influenza A/H1N1 2009 infection: FLU-CIN cohort study
Malcolm Simple1, Wei Shen Lim2, Pija Myles1, Joanne Enstone3, Malcolm Semple1, Wei Shen Lim2, Pija Myles1, Joanne Enstone3, Peter Openshaw4, Robert Read1, Bruce Taylor4, James McMenamin5, Barbara Bannister6, S.J. Brett, Karl Nicholson7, Jonathan Nguyen-Van-Tam1, 1Women’s and Children’s Health, University of Liverpool, Liverpool, United Kingdom; 2Respiratory Medicine, Nottingham University Hospital, Nottingham, United Kingdom; 3Epidemiology and Public Health, University of Nottingham, Nottingham, United Kingdom; 4Centre for Respiratory Infection - National Heart and Lung Institute, Imperial College London, London, United Kingdom; 5Infection and Immunity, University of Sheffield, Sheffield, United Kingdom; 6Intensive Care Medicine, Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom; 7Public Health Medicine, Health Protection Scotland, Glasgow, United Kingdom.

Introduction: Asthma was the commonest co-morbid illness in patients admitted to hospital with influenza A/H1N1. Yet patients with asthma were half as likely to die or require admission to level 2 (high dependency) or level 3 (intensive care).

Hypothesis: Asthma, rather than associated co-morbidities or treatments such as the use of steroids, is an independent factor for improved outcomes in influenza A/H1N1.

Methods: Between April 2009 and January 2010, FLU-CIN collected clinical, epidemiological and outcome data on patients with confirmed influenza A/H1N1 admitted to 75 UK hospitals.

We studied 1520 patients, of whom 480 (31.6%) were <16yrs. Asthma was the commonest co-morbid illness affecting 385 (25.3%) patients.

Findings: Patients with asthma had higher rates of dyspnoea, need for supplemental oxygen and severe respiratory distress than patients who did not have asthma but were significantly less likely to die or require level 2 or 3 care (11.2% vs. 19.8%; OR 0.51, 95% CI 0.36 to 0.72). Co-morbid illnesses were more frequent in patients with asthma (22.6% vs. 7.6%). There was no difference in the proportions with pneumonia (17.1% vs. 16.6%). The association of asthma with less severe outcome was unaffected by age, presence of co-morbidities, in-hospital anti-viral and/or antibiotic use. Adjusting for prior use of inhaled steroid changed the association with severe outcome by over 10% (OR 0.63, 95% CI 0.42 to 0.94). Adjusting for “delayed admission >4 days” had a similar effect (OR 0.63, 95% CI 0.42 to 0.95).

Conclusion: In multivariate analysis, the combination of prior inhaled steroid use and prompt admission to hospital (<4 days) explained the association of asthma with less severe outcome.
Experimental rhinovirus infection in moderate asthma

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Background: Rhinovirus (RV) is the most common cause for asthma exacerbations. Underlying mechanisms are poorly understood. A human model of experimental infection with RV has been introduced however studies have thus far only recruited mild asthmatics. In order to be more representative of those who experience virus-induced exacerbations there is a need to establish the safety of this model in moderate asthma.

Aim: To assess the safety of the RV challenge model in subjects with moderate asthma treated with inhaled corticosteroids.

Methods: Six subjects with moderately severe atopis asthma requiring maintenance inhaled corticosteroids were infected with RV16. Nasal lavage (NL) and clinic spirometry were performed on days 0,2,4,5,7,10. Symptom scores were recorded daily throughout the study. Clinical infection was confirmed using a combination of symptom scores, demonstration of RV16 RNA by RT-PCR in nasal lavage and at least a 4-fold increase in RV16 specific antibody titres on day 42.

Results: All 6 subjects developed symptoms of a common cold 24-48 hours prior to an increase in lower respiratory symptoms. This was accompanied by a drop in morning FEV1 (mean fall of 25%). Whilst all subjects increased their use of bronchodilator, no subjects required oral corticosteroid therapy. RV16 infection was demonstrated in NL in all subjects.

Conclusions: In this pilot study infection with RV16 in moderate asthma was well tolerated, consistent with previous studies. No unexpected adverse events or requirement for oral steroids occurred. The use of RV challenge in moderate asthma therefore appears safe. Results of future studies using this group of patients will better reflect those individuals with the greatest burden of disease.

P2499
Serum microRNA signatures identified in a genome-wide profiling predict the mortality of patients with sepsis

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1Department of Pulmonary Medicine, Jichi Medical School, Tochigi, Japan. 4,5Department of Internal Medicine and Cardiovascular Medicine, Jichi Medical School, Tochigi, Japan. 3Department of Cardiac Surgery, Jichi Medical School, Tochigi, Japan. 2Department of Internal Medicine, Jichi Medical School, Tochigi, Japan.

Purpose: Serum miRNAs are present and stable, reproducible, and consistent among individuals in the serum and plasma of humans and other animals. And they can be fingerprints of different diseases. We used genome-wide serum miRNA expression profiling analysis to investigate the role of serum miRNA in predicting prognosis of sepsis.

Patients and methods: According to the 28-day mortality, Solexa sequencing followed by individual quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assays was used to test the difference in levels of serum miRNAs between survivors and nonsurvivors. Then were Survivors and 9 nonsurvivors matched by age, sex, and stage for the early detection. The detected serum miRNAs were then validated in 92 sepsis patients (39 survivors and 53 nonsurvivors) and 24 healthy controls.

Results: Twelve serum miRNAs were found to be altered more than two-fold from Solexa sequencing between survivors and nonsurvivors group. qRT-PCR was preformed in 6 miRNAs (miR-206, miR-378, miR-223, miR-15b, miR-15a and miR-16) according to the previous studies. miR-223 (p=0.008<0.01), miR-15b (p=0.008<0.01) and miR-16 (p=0.009<0.01) were significantly difference between those two groups. Then APECESIcore score, SOFA score, CRP, PCT of those patients combining the three miRNAs extend asymptotically to logistic regression. Multiple logistic regression analysis showed that miR-223, APECESIcore and SOFA score were significantly associated with the mortality of sepsis patients.

Conclusion: miR-223, miR-15b and miR-16 from the serum may serve as a noninvasive predictor of the mortality of sepsis patients.

P2500
Reduction of oxidative stress in successfully treated patients with community acquired pneumonia (CAP), as measured by redox status of coenzyme Q10 (%CoQ10)

Terentiy M. Gorbunov1,2,3, Pavel Ogarkov1, Sergey Zhogolev1, Konstantin Jogolev2.

1Military Medical Academy, St. Petersburg, Russian Federation; 2Immunology and Microbiology, Military Medical Academy, St. Petersburg, Russian Federation

Aim: To study the efficacy of combined use of pneumococcal vaccine and supplementary preventive means.

Methods: Five groups of military servicemen numbering 120 to 240 persons received, in addition to pneumococcal vaccination, one of preventive means. Persons of the 1st group received influenza virus vaccine, the 2nd group received imudon, the 3rd group bronchomunal, the 4th group cytovir-3, the 5th group arbidol during 4-10 days. Comparative groups were in the same conditions as experimentation groups and received pneumococcal vaccine only.

Results: In 1 and 3 months after the onset of agents’ administration in all the groups in which supplementary preventive agents were administered together with pneumococcal vaccine, an incidence of pneumonia and acute respiratory infections was from 1.6 to 3.5 times lower than in the comparative groups. Thus, one and three months after imudon administration, its efficacy index against pneumonia was 3.5 and 2.2 respectively. The efficacy of supplementary agents was most marked during the first month following administration onset.

Conclusion: To prevent pneumonia in recruits, it is a good practice to use, together with pneumococcal vaccine, influenza virus vaccine, vaccinal immunomodulating agents (such as imudon, bronchomunal), immunocorrecting agents (such as cytovir-3), antiviral medications (such as arbidol) in first days following call-up.

5456s

MONDAY, SEPTEMBER 26TH 2011
The use of influenzal (IV) and pneumococcal (PV) vaccine in patients, staff and visitors at a university hospital in two periods

Pablo Fiscina, Vanina Martin, Fernanda Runundo, Gustavo Longo, Ileana Pampa, Carlos M. Luna. Pulmonary Diseases Division, Hospital de Clinicas, Universidad de Buenos Aires, Buenos Aires, Argentina

Aims: To determine the trend of IV and PV coverage for the at risk population comparing the years 2001 and 2010.

Methods: 1191 adults (507 in 2001 and 684 in 2010), including patients, relatives, health care workers, medical students and hospital employees, were interviewed at the hospital. They were asked about age, medical history, their knowledge about IV and PV and vaccination history. At risk population was considered according with the current national guidelines.

Results: Among the people with indications for IV, it was received by 50.1% in 2001 and 63.1% in 2010 (p < 0.001) and PV by 11.8% in 2001 and 20.7% in 2010 (p = 0.005).

National Guidelines in Argentina for IV and PV

<table>
<thead>
<tr>
<th>Indication</th>
<th>IV</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Cardiac</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Hepatic</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Renal</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Diabetes</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Immuno-Deficience/Compromise</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Health Care Worker</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

The trend of vaccination rate improved significantly for few indications; for IV in health care workers (21.2% vs. 77.7%, p<0.001) and in people with hepatic comorbidity (9.4% vs. 46.6%, p=0.017) and for PV only for those with pulmonary comorbidity (17.7% in 2001 vs 51.0% in 2010, p=0.004).

Analyzing 2001 and 2010 together, IV rate was higher in retired people >65 years old included in a social security program (PAMI) consisting in intensive advertising, free delivery and administration; than in those not included in such program (62.1% vs 46.4%, p=0.001).

Conclusions: Vaccination coverage remains low, particularly for PV. Improvement of IV and PV require better awareness, changes in clinical practice, delivery of IV and PV and vaccination history. At risk population was considered according with the current national guidelines.

P2506 Compliance with CURR-65 score and the consequences of no implementation

Qg Gu1, Hai-Yan Li2, Yi-Ping Zhou1, Ming Li1, Xiao-Ke Chen1, Hui Lu1, Hong-Lin Peng1, Hai-Qiong Yu1, Xia Chen1, Nian Lin1, Li-Hua Li1, Qiong-Zhou Zhao1, Mei Jiang1. 1Department of Respiratory Medicine, Affiliated Fattan Hospital, Guangdong Medical College, Shenzhen, China; 2Department of Primary Care, Affiliated Fattan Hospital, Guangdong Medical College, Shenzhen, China; 3Department of Radiology, Affiliated Fattan Hospital, Guangdong Medical College, Shenzhen, China; 4Guangzhou Institute of Respiratory Diseases (State Key Laboratory of Respiratory Diseases), First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

Background: The CURR-65 score is a simple well validated tool for the assess-ment of severity in community-acquired pneumonia (CAP). Whether it is used routinely is unknown. The aim of this study was to determine the frequency of use of the score in routine hospital practice and the consequences of no implementation.

Methods: A retrospective analysis of data from 1230 patients with CAP in a Chinese affiliated hospital of a medical college was performed.

Results: None of the patients with CAP had CURR-65 score applied at admission. 716 (58.2%) patients who had a CURR-65 score of 0 were unnecessarily hospitalized. 402 (32.7%) patients who had a CURR-65 score of 1 might be admitted unnecessarily. 14 (1.2%) patients who had a CURR-65 score of 3 or more were not admitted to critical care unit. The unnecessary total annual costs for managing CAP with CURR-65 score of 0 and 1 were estimated at $ 94512 and $ 6 410 4 in the hospital, respectively.

Conclusions: Non-compliance with the CURR-65 scoring tool in patients with CAP was observed in routine hospital practice. No implementation of the measure-ment of the score incurred inappropriate hospitalization and unnecessary costs.
the most frequent radiologic finding. CR is not a good tool to discriminate between BP and VP.

**P2508**

Metapneumovirus pneumonia in allogeneic stemcell transplant recipients
Adrian Fruhwald1, Dominik Heim2, Martin Gerdes2, Christoph Bucher2, Hans Hirsch2, Michael Tamm3, 1 Clinic of Hematology, University Hospital of Basel, Basel, Switzerland; 2 Clinic of Microbiology, University Hospital of Basel, Basel, Switzerland; 3 Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital of Basel, Basel, Switzerland

Infectious and noninfectious pulmonary complications are frequent in allogeneic stemcell transplant recipients (SCT) and associated with a high morbidity and mortality. Metapneumovirus (MPV) has recently been recognised to cause lethal infections in immunocompromised patients. Following an index case with fatal outcome we included PCR for Metapneumovirus in the routine work-up of BAL performed in hematological patients with pulmonary symptoms. We analysed the clinical presentation and outcome of 8 allogeneic stemcell transplant recipients with a median of 45 year observed over a period of 12 months. Median Time to pulmonary MPV infection was 473 days after SCT. 6 of 8 patients were under immunosuppressive therapy for GVHD and 4 of them had biopsy proven bronchiolitis obliterans. All patients suffered from cough and/or fever. CT scan of the chest revealed a groundglass pattern in all but one cases. There were nodules in five cases and alveolar-interstitial infiltrates in also 5 cases. Enlarged lymphnodes were only present in one patient. In one patient there was concomitant infection with moraxella cathartalis. Two patients showed viral double infection in the BAL (MPV/coronavirus; MPV/rhinovirus). All patients were hospitalized because of marked symptoms or hypoxemia. Anemia was the most frequent side-effect of antiviral treatment. 7 out of 8 patients recovered. The patient who died had developed MPV pneumonia within one month following SCT.

Conclusion: Metapneumovirus pneumonia is not uncommon following allogeneic stemcell transplantation. Typical clinical features include fever, cough and a groundglass pattern on chest CT scan. Most patients recover under treatment with immunoglobulins and ribavirin.

**P2509**

Non-tuberculous infections in patients with TNF-alpha-antagonist treatment
Bahar Ozcelik, Penbe Cagatay, Zeki Kilicaslan, Ziya Gulbaran.

In recent years the use of TNF antagonist drugs for many diseases such as rheumatological diseases has increased. As a complication of these treatments, non-tuberculous infections are not frequent despite the absence of control measures and they were mostly upper respiratory tract infections. Our study indicates that non-tuberculous infections were detected. In an asthmatic patient also frequent infective attacks were observed. Thirtyseven definitive cases were found, 21 (56%) were male, 13 (35%) were Health Care Associated Pneumonia. LD was severe in 26 (70%) cases, which belonged to the highest Pneumonia Severity Index classes (IV-V). At the admission an acute respiratory failure (PaO2/FiO2 < 200 or SpO2 < 90% or PaO2 < 60 mmHg) was found in 18 patients (48%), 4 of these met ARDS criteria and non invasive-ventilation (CPAP) was necessary in 7 (19%). There were no significant differences in demographic and clinical features between the two groups (not-ARF vs ARF), see table.

Only one patient required an ICU admission and one patient died (3%). An appropriate antibiotic therapy was initiated in all patients on admission day. In conclusion, though no warning prognostic sign has been found yet, clinicians should remain vigilant about the respiratory complications in patients with Rheumatoid arthritis.

**P2511**

Clinical stability in patients with community-acquired pneumonia (CAP) in hospitalized patients over 18 years of age in the unit of Pulmonology and Intensive Care, University Hospital of Basel, Basel, Switzerland

Clinical stability (CS) defined as normalization of vital signs, is often used to manage patients with CAP. The aim of our study was to identify the time to resolution of abnormalities in vital signs (heart rate - HR, systolic blood pressure - SP, respiratory rate - RR, oxygen saturation - SATO2 and axillaries temperature - T), ability to eat (AE), and mental status (MS) in patients with CAP (n=118). The patients divided in 2 groups, from 18-65 years old (n=65)- first group, and older ≥ 65 (n=53 - second group). We compared parameters of CS in groups in the first day, and the time normalization of CS between groups (HR ≤ 100 beats/min, SP ≥124 mmHg, RR ≤ 24 breath/min, SATO2 ≥90%, T ≤ 37.2°C).

Results: We found in first group, in first day of hospitalization, average values of HR=115 beats/min, SP=103mmHg, RR=26 breaths/min, SATO2=93% T=38,3°C, in the second group HR=96 beats/min, SP=88 mmHg, RR=28 breathes/min, SATO2=96%, T=37,4°C. In 15 patients second group had mental confusion. The median time to stability in first group was 1 day for HR, SP and RR, and 2 days for SATO2, 3 days for T and 5 days for AE. The median time to stability in second group was 1 day for HR, SP, T, and 3 days for RSATO2 and 8 days for AE.

Conclusion: The older patients had slowly time to stability for SATO2, RR and MS, and smaller T and HR in first day.

**P2512**

Cpmydia pneumoniae (Cp)-specific IgE is associated with asthma severity
Adrian Fruhwald1, Dominik Heim2, Martin Gerdes2, Christoph Bucher2, Hans Hirsch2, Michael Tamm3. 1 Clinic of Hematology, University Hospital of Basel, Basel, Switzerland; 2 Clinic of Microbiology, University Hospital of Basel, Basel, Switzerland;

Cp pneumoniae (Cp)-specific IgE is associated with asthma severity and whole blood Cp DNA by PCR, and associations with asthma severity and antibiotic treatment outcomes; nested case-control study of asthma cases and non-asthma controls.

Aims: To investigate bacterial allergy as a potential mechanism for Cp-associated asthma.

Methods: Practice-based prevalence study of serum Cp IgE by immunoblotting and whole blood Cp DNA by PCR, and associations with asthma severity and antibiotic treatment outcomes; nested case-control study of asthma cases and non-asthma controls.

Results: We studied 66 asthma subjects (mean age 40.9 years, range 7.5-79.8 years, 56%, 15% co-existing COPD). Cp IgE was detected in 33 (50%) and Cp DNA in 16 (24%). 88% of Cp DNA pos subjects were Cp IgE pos (P=0.011). 4 (22%) of 18 subjects with intermittent asthma were Cp IgE pos compared to 30 (63%) of 48 with persistent asthma (P=0.005). We also found a significant “dose-response” relationship (Table).

<table>
<thead>
<tr>
<th>Category</th>
<th>Intermittent, Mild persistent, Moderate persistent, Severe persistent, P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>27</td>
<td>15</td>
</tr>
</tbody>
</table>

| Cp IgE pos, n (%) | 4 (22) | 4 (67) | 14 (52) | 12 (80) | 0.0088 |

A nested case-control study detected Cp IgE in 10 (53%) of 19 asthma cases and in 15 (75%) of 20 non-asthma controls (P<.15).
273. Infection in the immunocompromised host: infrequent aetiologies

P2514
Experimental fatal pneumonia due to Burkholderia cepacia: Differential involvement of toll-like receptors (TLRs) 4 and 5
Viviane Ballot1,2, Heidi Nagel1, Reuben Rampal3, Mustapha Si-Tahar1,2, Michael Chizeck1,2,3
1Défense Innée et Inflammation, Institut Pasteur, Paris, France; 2U574, INSERM, Paris, France; 3Department of Medicine, University of Florida, Gainesville, United States

As shown in a previous study (Ventura et al., 2009), MyD88, a key downstream adapter for most of the TLRs, is involved in the inflammatory response responsible to the death due to B. cepacia pneumonia. The aim of the present study was to determine which TLRs were involved in this response. We specifically focused on the TLRs 4 and 5, as these two receptors are the main ones involved in the recognition of P. aeruginosa, a flagellated Gram-negative bacterium like B. cepacia.

Mice deficient for TLR4, TLR5 or both were infected intratracheally with a sus-##

P2515
Sensitivity to bordetella pertussis in asthmatic patients
Yohei Yatagai1, Takehumi Saito1, Yasuhiro Umetsu2, Shimao Fukai 1
1Department of Respiratory Medicine, Nagaoy City University Hospital, Nagaoy, Aichi, Japan

Background/Aim: Asthmatic patients may complicate with pertussis more fre-##

P2516
Chronic pulmonary aspergillosis: Characteristics of 30 nonimmunocompromised patients
Boubou Camara1, Bernandette Lebeau2, Christel Saint-Raymond 1, Gilbert Ferret1, Jaques Cadranel 2, Christophe Pison 1
1Clinique de Pneumologie, Hôpital Michallon, Grenoble, France; 2Laboratoire de Parasitologie-Mycologie, Hôpital Tenon, Paris, France

Introduction: Chronic pulmonary aspergillosis (CPA) is a severe respiratory in-##

CONCLUSION: We speculate the humoral immunoreaction to B. pertussis could be suppressed in asthmatic patients.
during the development process. It seems very possible that appearances and disappearances of air-fluid levels are related to exacerbation of CPA. But it has yet to be determined.

**Aims and objectives:** To demonstrate relationship between air-fluid levels and acute exacerbation of CPA.

**Method:** We analyzed retrospectively our patients with acute exacerbation of CPA during the period from 2001 to 2010 at Ibarakihigashi National Hospital.

**Results:** We experienced 93 cases of acute exacerbation of CPA and the incidence of appearance of air-fluid level was 34% (32 patients). At deterioration, new infiltrative shadows appeared on separate sites from primary cavities in 33 patients (35%), and 27 of them previously had air-fluid levels in their cavities. In 15 patients, fluid volume in their cavities increased before acute exacerbation. Eight of them showed new infiltrations away from primary lesions and fluid volume in their cavities decreased after acute exacerbation. Corticosteroids drastically improved their infiltrations on chest radiograph, blood findings and medical conditions in 5 out of 8. But in 3 patients, corticosteroids didn’t improve their conditions.

**Conclusion:** The air-fluid levels in cavities were associated with acute exacerbation of CPA. In some cases, patients showed new infiltrations away from cavities with decreased fluids during acute exacerbation. It suggested that fluids in cavities, which contained substances produced by Aspergillus, might damage separate sites from primary cavities.

**P2518**

**Aspergillus-PCR in bronchoalveolar lavage for detection of invasive fungal disease in immunocompromised patients**

Michael Thomas1, Jorg Haller1, Lilian Junker1, Peter Grendelmeier1, Michael Tamm1, Daiana Stolz 1, 2

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**Introduction:** Invasive fungal disease (IFD) is a frequent and serious infectious complication in neutropenic patients. We evaluated the diagnostic accuracy of conventional nested PCR in the bronchoalveolar fluid to diagnose IFD in severe immunocompromised patients.

**Methods:** 191 consecutive patients undergoing bronchoscopy for suspected pulmonary infection were included. The probability of IFD was estimated according to the standard EORTC/NIAID classification and on clinical grounds as independently assessed by a pulmonary specialist and hematologist. Conventional nested PCR to detect aspergillus fumigatus, flavus, niger, gausius, terreus and tannarii were applied to 2 ml bronchoalveolar fluid.

**Results:** In 50.5 (9-19.80), 116 were male. There were 129 patients with hematological conditions, 26 solid organ transplant recipients, 24 auto immune disorders, and 12 HIV. A total of 111 (58.1%) of the patients were on anti-fungal therapy at the time of bronchoscopy. According to the EORTC/NIAID classification, 2 (1%) had proven, 8 (4.2%) probable, 43 (22.5%) possible and 138 (72.3%) no IFD. Nested PCR for Aspergillus was positive in 55 cases (28.8%) – 0/2 in proven, 4/8 in probable, 10/43 in possible and 41/38 in no IFD. Anti-fungal therapy did not significantly influence PCR results (p=0.749). Irrespective of the EORTC/NIAID criteria, there was a strong clinical suspicion of IFD in 53 (27.7%) cases. From those, only 15 (28.3%) had a positive PCR.

**Conclusion:** Nested aspergillus PCR in the bronchoalveolar lavage seems to be of limited usefulness for detection of invasive fungal disease in immunocompromised patients.

**P2519**

**Role of bronchoscopy in non-HIV immunocompromised patients**

Hugh Jp, Chris Kosky, Anne Collett. *Thoracic Medicine, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom*

**Background:** Non-HIV immuno-compromised patients with suspected chest sep sis commonly undergo bronchoscopy to aid microbiological diagnosis.

**Aims:** Characterise non-HIV immuno-compromised patients undergoing bronchoscopy at a London hospital to assess the diagnostic utility of this procedure with a focus on results leading to treatment changes.

**Methods:** Clinical records of all patients undergoing bronchoscopies over a 14-month period were retrospectively reviewed. The diagnostic yield was calculated using the total number of bronchoscopies as the denominator. A positive result was defined as any positive culture (viral, fungal, bacterial) or diagnostic pathology. Using the clinical notes and prescription charts the percentage of treatment changes following bronchoscopic results was calculated.

**Results:** 43 bronchoscopies were carried out in this group. Underlying diagnoses were haematological malignancy (27), organ transplant (10), solid organ tumour (2), rheumatological (4). The most common indication was suspected infection (76.7%); fungal infection was suspected in 46.5%. The overall diagnostic yield was 51.2% (95% CI, 36.1-66.3%). Many of the positive samples were for virus (10) followed by positive bacterial cultures (8). Few samples were positive for fungus (2). Therapy was changed after 18.6% (95% CI, 6.8-30.4%) of all bronchoscopies. The total complication rate was 4.6% (95% CI, 1.7-11.1%); both cases due to controllable bleeding.

**Conclusions:** The most common underlying diagnoses were haematological malignancies. Fungal chest infection was frequently suspected, but the fungal organism yield was low; treatment decisions were based on clinical and radiological findings. Total diagnostic yield was similar to published data.

**P2520**

**Viological analysis on bronchoalveolar lavage fluid (BALF): Diagnostic yield and indications**

Jean-Sébastien Poinet1, Stéphane Jouneau1, Sophie Minjolle2, Pierre Tattevin2, Philippe Delaval3, Benoît Dresuir1 3

*Respiratory Medicine Department, Ponchailou University Hospital, Rennes, France; 2Bacteriology and Virology Department, Ponchailou University Hospital, Rennes, France.*

**Introduction:** BAL is a major diagnostic tool in infective lung diseases. Viral respiratory infections are a frequent cause of asthma and COPD exacerbations as well as severe pneumonia.

**Aims:** To analyze the characteristics of subjects with positive virological analysis of BALF and to define the best indications.

**Methods:** We retrospectively studied all virological analysis (immunoﬂuorescence, viral culture and PCR) performed on BALF in 2008 at Rennes University Hospital, France. We compared characteristics of patients with positive vs negative virological analysis of BALF.

**Results:** 232 BAL were performed in 212 patients. Seventy BAL were positive (30%), including 84 viruses: HSV1 (27), CMV (23), EBV (17), HHV6 (12), RSV (3), rhinovirus (1) and adenovirus (1). Immunocompromised patients represent 83% of all positive BAL. Immunosuppression (HPV patients, corticosteroids > 10 mg/day for ≥ 3 weeks or immunosuppressive therapy) and ground glass attenuations on chest CT-scan were more present in patients with positive virological BALF compared to negative: respectively 82.9% vs 46.9%; p<0.0001 and 65.8% vs 43.7%; p=0.006. There were no significant differences in demographic and clinical criteria (age, gender, fever, dyspnea, cough, hemoptysis). Pneumonia in immunocompromised subjects was the most frequent indication of BALF viral analysis (55%) with a diagnostic yield of 44%. None of the 17 virological analyses of BALF performed for assessment of diffuse infiltrative lung disease was positive.

**Conclusion:** Pneumonia in immunocompromised hosts seems to be the preferential indication of virological analysis of BALF, especially when chest CT-scan demonstrates ground-glass attenuations.

**P2521**

**The role of fiberoptic bronchoscopy (FOB) in the management of pulmonary disease in the immunocompromised (IC) host**

Sheinongt Saha1, Joanne Creaser2, Charlie Elliott1, Stephen Bianchi1, 2

*Sheffield Thoracic Institute, Sheffield Teaching Hospital NHS Trust, Sheffield, United Kingdom; 1Clinical Effectiveness Unit, Sheffield Teaching Hospital NHS Trust, Sheffield, United Kingdom*

**Introduction:** FOB is a recognised tool in evaluating IC patients with lung disease. It is often utilised after administration of antimicrobial therapy which potentially affects diagnostic rate.

**Aims:** Assessment of the role of FOB in IC patients presenting to a UK hospital between December 2007-09.

**Method:** Retrospective data was reviewed for 48 patients.

**Results:** 19/48 (39.6%) presented with leucopenia (WCC <3.5 x 109/l), 18/48 (37.5%) with neutropenia (PMN <1.7 x 109/l) and 30/48 (62.5%) had lymphopenia (LØ <1.0 x 109/l). Significant desaturation (requiring unplanned intervention) occurred in 7/48 (14.6%) patients. 30 day mortality was 11%. Positive bacterial cultures were obtained in 10/48 samples (21%). Organisms: Proteus, H Influenza, Ps.Aeruginosa, Klebsiella, S.Aureus, S.Maltha. Coagulate negative staphylo cocci, enterococcus, E.coli and Group B streptococcus. 17/48 (35%) patients had a change in management directly resultant from BAL bacterial culture. Positive fungal cultures were identified in 16/48 (33.3%) samples. Species: C.Albicans, Saccharomyces, Aspergillus and C.Glabata. 8/48 (17%) patients had treatment altered based on BAL fungal culture. Positive virology identified in 10/48 patients (rhinovirus, CMV, HSV type 1, EBV, coronavirus). 4/48 (8%) patients had resultant changes in treatment. 7/45 (16%) patients were positive for Pneumocystis jirovecii with treatment change in 5 patients. In 40.5% of cases a treatment change was based on FOB/BAL results.

**Conclusion:** FOB/BAL has a major impact on the treatment of IC patients with pulmonary disease. Early respiratory involvement prior to broad spectrum antimicrobial therapy may have increased FOB yield.

**P2522**

**In vivo imaging of rat experimental invasive pulmonary aspergillosis using fibred confocal fluorescence microscopy**

Helene Morisset1, Loraine Heyman1, Mathieu Salau1, Loic Favence2, Jean Michel Piccione1, 2

*Laboratoire Quantif E LITIS, EA 4108, Faculté de Médecine et de Pharmacie, Rouen, France; 1Laboratoire de Parasitologie Expérimentale, EA 324, Faculte de Médecine et de Pharmacie, Rouen, France, 2Service d’Anatomopathologie, Centre Henri Becquerel, Rouen, France*

**Rational:** Aspergillus fumigatus is responsible for life-threatening respiratory
infections in immunosuppressed patients. Early diagnostic would improve the prognosis. Fibred confocal fluorescence microscopy (FCFM) is a new endoscopic tool that enables in vivo microscopic imaging of the distal lung in situ. In this study we tested the hypothesis that FCFM could be utilized for the visualization of pulmonary aspergillosis infection in vivo, in situ.

Methods: Experimental pulmonary invasive fungal infections were induced in immunosuppressed rats using a wild strain of A. fumigatus (n=6) a wild strain of Geosmithia argolea (n=6) and a fluorescently transformed Tag-RFP A. fumigatus strain (n=6). Subpleural areas of pulmonary infection and control lungs were imaged using FCFM through a chest wall window.

Results: From the fungal strains, only hyphae of the Tag-RFP A. fumigatus were detectable by FCFM both in vitro and in vivo. In vivo, hyphae of the Tag-RFP Aspergillus strain were visualized by FCFM in 100% of the lung infection with a specificity of 100% (6/6) compared to normal lung and other fungal infection. Using non fluorescent strains, a specific local infiltration of fluorescent cells could be localized in half fungal subpleural microabcesses (Se 100%;Spe 58%).

Conclusion: FCFM represents the first imaging technique of pulmonary aspergillosis in real time and in vivo. It provides a new tool to study host-pathogen interactions and may help for early diagnosis of pulmonary aspergillosis in vivo.

P2523
Clinical characteristics of surgically-diagnosed pulmonary cryptococcosis
Akihiro Ito, Hiromasa Tachibana, Tadashi Ishida. Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki-City, Okayama, Japan

Background: Pulmonary cryptococcosis is a type of pulmonary mycosis that can be asymptomatic and determined only as an abnormal shadow on X-ray film. Because differentiating pulmonary cryptococcosis nodules from lung cancer is difficult, some patients must be surgically diagnosed. Furthermore, whether surgically-diagnosed pulmonary cryptococcosis should be treated remains controversial.

Objectives: The aim of this study was to evaluate whether we can differentiate pulmonary cryptococcosis from lung cancer, and if it should be treated after surgery.

Methods: We retrospectively analyzed 17 patients with surgically-diagnosed pulmonary cryptococcosis at the 1153-bed Kurashiki Central Hospital (a tertiary facility) for ten years from April 1994 and November 2009.

Results: The 8 male and 9 female patients (median age, 56 years; range, 36 to 71 years) included 2 with diabetes mellitus and 2 who were treated with steroids. Eleven patients who underwent thoracic bronchoscopy before surgery were not diagnosed. Only one of six patients was positive for Cryptococcus antigen. The X-rays revealed nodules or a mass in all patients and none had an infiltration shadow. Thirteen patients had a single nodule. Only one patient was administered with antibiotics and none of the 17 patients relapsed.

Conclusions: To differentiate a single nodule of pulmonary cryptococcosis from lung cancer was difficult, rendering surgery as the sole definitive diagnostic option. None of our patients relapsed including four who were immunocompromised, indicating that treatment is not a necessary component of follow-up after surgical diagnosis of pulmonary cryptococcosis.

P2524
Alterations of surfactant phospholipids in lungs with chronic recurrent respiratory chlamydial infection
Petra Reinhold1, Michael Rothe2,1. Institute of Molecular Pathogenesis, Friedrich-Loeffler-Institut, Jena, Germany; 2Lipidomics GmbH, Campus Berlin-Buch, Berlin, Germany

This study aimed to identify alterations in the composition of surfactant phospholipids (PLs) with respect to chronic respiratory chlamydial infection. Broncho-alveolar lavage fluid (BALF) was sampled from 13 calves with naturally acquired chronic, but clinically latent, chlamydial infection (C. pecorum and/or C. abortus). Calves without chlamydial infections of the same age and kept under identical conditions served as controls (n=12). Prior to BAL, exhaled breath condensate (EBC) was collected in each animal. In both BALF and EBC, phospholipids were measured (tripletquad tandem mass spectrometer). Phosphatidylcholine (PC), being the main phospholipid in pulmonary surfactant and measurable in both EBC and in BALF samples, was significantly reduced in animals with chlamydial infections. In addition, concentrations of lysophosphatidylcholin, phosphatidylethanolamine (PE), and phosphatidyl ethanolol (PI) were significantly reduced in BALF (not measurable in EBC). Altogether, total concentration of phospholipids was significantly lower but ratios between PC/PE and PG/PE (PG: phosphatidylglycerol) were significantly higher in calves with chlamydial infection compared to controls.

In conclusion, chronic respiratory infections with chlamydiae were associated with significant alterations in the phospholipid composition of the epithelial lining fluid of the lung. Since surfactant is involved in both lung compliance as well as alveolar cleavage, results of this study indicate chlamydia-associated deterioration of pulmonary mechanics and depressed alveolar defense mechanisms despite the absence of clinical signs or pulmonary symptoms.

P2525
Pulmonary and systemic inflammation in a domestic animal model of respiratory chlamydia phila pusi ci infection: Evaluation of dose-response relationships
Carola Ostermann1, Annette Vogel1, Wieland Schroeder2, Angela Berndt1, Evelyn Schubert1, Konrad Sachse3, Petra Reinhold1, Evelyn Schubert1, Konrad Sachse1, Petra Reinhold1. 1Institute of Molecular Pathogenesis, Friedrich-Loeffler-Institut, Jena, Germany; 2Institute of Bacteriology and Mycology, Veterinary Faculty, University of Leipzig, Leipzig, Germany

This study aimed to evaluate dose-response relationships of pulmonary and systemic inflammation with respect to a new model of respiratory Chlamydia phila pusi ci infection introduced recently. Four infection dosages (inclusion forming units of strain DC 15) were administered intrabronchially per calf: 10⁷ (n = 4), 10⁶ (n = 4), 10⁵ (n = 4), 10⁴ (n = 2). Control animals received medium (n = 4) or the inactivated strain (10⁵; n = 6). Pulmonary inflammation was assessed by analysing broncho-alveolar lavage fluid (BALF) 2-3 days post inoculation (dpi). As biomarkers of systemic inflammation, acute phase proteins (LBP=lipopolysaccharide binding protein, Hp= haptoglobin, CRP) were measured in serum samples.

After challenge with viable chlamydiae, most of inflammatury markers followed dose-response curves (Table). In the lung, recruitment of neutrophil granulocytes increased with increasing doses. In blood, LBP was superior in reflecting host response.

Conclusion: In conclusion, pulmonary and systemic inflammation varied from mild (10⁴ ifu) to severe (10⁸ ifu). For further studies, inoculation of 10⁸ ifu per animal is recommended to induce a clinically apparent respiratory disease with local and systemic host responses.

P2526
Radiological features and their associations with clinical and laboratory findings in adults with mycoplasma pneumoniae pneumonia
Qi Guo1, Hai-Yan Li2, Yi-Ping Zhou1, Ming Li1, Xiao-Ke Chen1, Hui Liu1, Hong-Lin Peng1, Hui-Chao Ye1, Nian Liu1, Li-Hua Liang3, Qing-Zhou Zhao1, Mei Jiang1, 1Department of Respiratory Medicine, Affiliated Fudan University, Guangdong Medical College, Shenzhen, China; 2Department of Primary Care, Affiliated Fudan University, Guangdong Medical College, Shenzhen, China; 3Department of Radiology, Affiliated Fudan Hospital, Guangdong Medical College, Shenzhen, China; 4Department of Radiology, Affiliated Fudan Hospital, Guangdong Medical College, Shenzhen, China; 5Department of Respiratory Diseases (State Key Laboratory of Respiratory Diseases), First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

Background and objective: The factors determining severity in Mycoplasma pneumoniae pneumonia and to determine their associations with clinical and laboratory findings.

Methods: A sixty-month retrospective study of 372 adult patients with M. pneumonia pneumonia was carried out. The diagnosis of M. pneumoniae pneumonia was made by the indirect microparticle agglutinn assay. We collected the radiological findings and assessed their associations.

Results: Ground-glass opacity was observed in 344 patients (92.5%), unilobar opacity in 316 patients (84.9%), and lower lobe involvement in 288 patients (77.4%). There was a significant increased odds ratio for multilobar opacity in male patients (OR, 3.279; p<0.001; 95% CI, 1.98 - 5.41). The patients with multilobar opacity had older age (p<0.001), higher CURB-65 scores (p<0.014), and more costs ($768.22±243.93 vs. $610.76±299.72, p<0.001).

Conclusion: Using a wild strain of M. pneumoniae as inoculum increased with increasing doses. In blood, LBP was superior in reflecting host response.

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Chlamydial infections are a known problem in cattle farming. We want to find out whether they are related to chronic respiratory illness in farmers. We selected 48 dairy farms with a history of occurrence of chlamydial infections. Nasal and vaginal swabs, milk and fecal samples and paired sera were obtained from 5 cows of each farm. The presence of chlamydial was analysed by rtPCR, by the ArrayTube DNA microarray test and paired sera were examined using an ELISA. The farmers were clinically examined by lung function testing, serology, allergy skin test, and their induced sputum was rtPCR tested.

The analysis of 48 farms showed that in 31 (64.6%) farms at least 1 sample from at least 1 cow was positive in rtPCR and 12 (25%) farms were positive only by ELISA. Chlamydia (C.) psittaci and C. pecorum were the most frequently identified species. At one farm, Chlamydia trachomatis was identified in cattle. So, far 39 individuals have been examined. 12 had respiratory symptoms and 3 were positive in serology. C. pneumoniae IgA occupied in 15 (38.5%) subjects and IgG in 26 (66.7%). Only 2 persons were positive for C. psittaci IgG. In 5 (12.8%) human sputum samples Chlamydia trachomatis was identified.

We found a prevalence of 64.6% (rtPCR), which is a wide dissemination of chlamydial infections in cattle herds. In humans, we found signs of an immune reaction against zoonotic C. psittaci in 2 subjects, which had regular contact to birds. Of these 2 farms were tested negative.

The presence of Chlamydia trachomatis in 5 sputum samples is remarkable and interesting and needs further investigation, as well as the detection of Chlamydia trachomatis of 4 cows. The farmers of this farm have not yet been examined.

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Chlamydial infections are a known problem in cattle farming. We want to find out whether they are related to chronic respiratory illness in farmers. We selected 48 dairy farms with a history of occurrence of chlamydial infections. Nasal and vaginal swabs, milk and fecal samples and paired sera were obtained from 5 cows of each farm. The presence of chlamydial was analysed by rtPCR, by the ArrayTube DNA microarray test and paired sera were examined using an ELISA. The farmers were clinically examined by lung function testing, serology, allergy skin test, and their induced sputum was rtPCR tested.

The analysis of 48 farms showed that in 31 (64.6%) farms at least 1 sample from at least 1 cow was positive in rtPCR and 12 (25%) farms were positive only by ELISA. Chlamydia (C.) psittaci and C. pecorum were the most frequently identified species. At one farm, Chlamydia trachomatis was identified in cattle. So, far 39 individuals have been examined. 12 had respiratory symptoms and 3 were positive in serology. C. pneumoniae IgA occupied in 15 (38.5%) subjects and IgG in 26 (66.7%). Only 2 persons were positive for C. psittaci IgG. In 5 (12.8%) human sputum samples Chlamydia trachomatis was identified.

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P2532 Acute LRT infections among patients with shingles
Lidia Zabaznoska, Vesna Semenakova, Sushma Bogojeva. Respiratory Diseases, Clinic of Infectious Diseases, Skopje, Macedonia, The Former Yugoslav Republic of.

Herpes Zoster is reactivation of VZV infection, triggered by stress, surgical inter- vention or lack of the immunocompetency. This intraganglionic latent viral RNA reactivation preceded the viral migration through the neural axons up to the asso- ciated dermatone causing balanitic cell degeneration, multinuclear cell expression with intranuclear inclusions, simultaneous inflammatory local reaction, finally expressed with characteristic shingles vesicles.

Material and methods: In a six year long period (2004-2010), 52 patients with shingles were hospitalized, 19 (36%) were immunocompromised due to immuno- suppressive therapy, lymph reticular malignant illness, HIV infection; 23 (44.4%) patients with shingles had LRT inflammation sings.

Results: Based on the clinical symptoms and standard blood, biochemical, radi- ological, bacteriological, serological testing’s parallel bacterial LRT inflammation was proven among 20 of 23 patients (86.9%), or 38.46% of 53 patients. This group of 20 with 27.2% bacterial inflammation includes 9 immunocompromised (85.7%) and 11 immunocompetent (55%) patients. Severe pulmonary inflammation had 6 (66.6%) of 9 immunocompromised (one of them nosocomial, transferred from the haematology clinic) and 5 (45.4%) of 11 immunocompetent, or 6 (30%) of 20 and 5 of 20 (25%).

Conclusions: The severity of the dermal expression as well as LRT inflammation was evident among immunocompromised patients. Their hospital treatment was prolonged, from 17 days up to 7 weeks (average 23 days) compared to immunocompetent patients with shingles and LRT inflammation (11-27 days-average 14 days). Antimicrobial (antibiotic/antiviral) therapy has empirically installed from the very beginning of hospital treatment, additionally improved where needed.

P2533 Clinical and evolutive patterns of respiratory infections in patients with HIV/AIDS from Timis County, Romania
Iosif Marincu, Lucian Negruittu, Stefan Mihaiuta, Ioan Iacobiciu, Nicoleta Berciu, Carmen Alexiou, Ioana Tudor, Adriana Neghina. Department of Pulmonology, University of Medicine and Pharmacy, Timisoara, Romania

Background: Acute respiratory diseases are part of opportunistic infections de- veloped by patients with HIV/AIDS due to immunosuppression. The present study aims evaluating the clinical and evolutive patterns of acute respiratory infections in patients with HIV/AIDS.

Methods: The authors have retrospectively analyzed 82 patients with HIV/AIDS and acute respiratory diseases admitted at Clinic of Infectious Diseases. The posi- tive diagnosis was based on clinical elements, biological parameters (erythrocyte sedimentation rate, leukocyte count, fibrinogen, C-reactive protein, sputum culture, etc) and paraclinical elements (chest radiography, spirometry).

Results: From the study group, 52 patients with acute respiratory diseases (p<0.04) have been registered: 10 cases (12.19%) had bacterial pneumonia, 8 (9.75%) had interstitial pneumonia, 4 (4.87%) had fungal pneumonia, 8 (9.75%) had acute bronchitis, 11 (13.41%) had influenza, 7 (8.53%) had acute angina and 4 (4.87%) had pulmonary tuberculosis. The etiological agent has been isolated in 21 cases: 7 with Streptococcus pneumoniae, 4 with Staphylococcus aureus, 2 with Klebsiella pneumoniae, 4 with Pneumocystis jirovecii and 4 with Mycobacterium tuberculosis. In 54 cases, CD4-cell count was less than 200 cells/mm³ and 28 cases (p<0.05) over 200 cells/mm³. Under specific therapy and antiviral treatment, the clinical outcome has been favourable in 50 cases, only 2 cases died with pulmonary tuberculosis.

Conclusion: The detailed study of the clinical and evolutive patterns of respiratory infections in patients with HIV/AIDS allows timely implementation of specific therapy and prophylaxis in this population group with multiple risks.

P2534 Health status impact of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis
Barbara Hampel1, Olaf Schoeman2, Peter Reimnitz3, Paul Jones4, Robert Wilson5.
1Global Clinical Development Antineoplastics, Bayer Schering Pharma AG, Berlin, Germany; 2Global Development, Bayer Schering Pharma AG, Berlin, Germany; 3Global Clinical Development, Bayer Schering Pharma AG, Wuppertal, Germany; 4Division of Clinical Science, St George’s, University of London, London, London, United Kingdom; 5Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom

Introduction: Potentially pathogenic microorganisms (PPMs) frequently colonize lungs of bronchiectatic patients, often leading to pulmonary exacerbations. This phase II randomized, double-blind study assessed the safety and efficacy of ciprofloxacin dry powder for inhalation (DPI) – a formulation (PulmoSphere™) using the T326 inhaler – over 28 days in patients with sputum culture positive for predefined PPMs.

Objective: To test the effect of ciprofloxacin DPI on bacterial load and health status in non-cystic fibrosis bronchiectasis (non-CF BE) patients.

Methods: 124 adult, non-CF BE patients (mean baseline characteristics: age 63, 34.4% male, FEV1 56% of predicted) received 32.5mg ciprofloxacin (50 mg ciprofloxacin DPI) or matching placebo twice daily for 28 days with a 56-day follow-up. In addition to the primary endpoint (reduction in total bacterial load in sputum at end of treatment [EOT]), patient-reported health status was assessed with the St George’s Respiratory Questionnaire (SGRQ).

Results: Ciprofloxacin DPI reduced bacterial load at EOT (~3.6 vs. ~0.3 logs, p<0.001). The difference in mean SGRQ total score between active and placebo was ~3 (p=0.059, 95% confidence interval ~7.3 to 0.1), close to a clinically relevant (~1) improvement. The trend lasted for 4 weeks after EOT (difference ~3.0) but was not maintained at 8 weeks after EOT (difference ~0.83). SGRQ domain scores, responder and per-protocol analyses confirmed the trend.

Conclusions: Ciprofloxacin DPI clearly trended towards improving patient- reported health status in non-CF BE measured with the SGRQ, which lasted for 4 weeks after treatment finished. Further study is required to confirm the results.

P2535 Pseudomonas aeruginosa sensitivity changes to antibiotics under the influence of dissolved ozone
Alia Plotnikova1, Igor Belyanin2, Lubov Selina2, Evgenii Shmelev2.
1Microbiology, Central TB Research Institut, Moskow, Russian Federation; 2Microbiology, The Medical Center of the Help to Invalids without, Moskow, Russian Federation; 3Microbiology, Central TB Research Institut, Moskow, Russian Federation

Aim: To study the sensitivity changes of clinical strains of organisms producing beta-lactamases to antibiotics under the influence of dissolved ozone (pO3).

Methods: We studied 20 Pseudomonas aeruginosa strains resistant to antibiotics of penicillin line. A suspension was prepared from the culture of each strain (1-2×10⁷/ml) and treated with dissolved ozone (pO3 2mg/m³) during 5-10.15 min. Then, the strains treated with pO3 were cultured on Muller-Hinton agar containing a strain resistant antibiotic. The same strain that had not been treated with pO3 was also cultured on the same agar containing the same antibiotic (control). In a day after incubation by 37ºC we recorded the result of the diameter zone of growth inhibition round the antibiotic disk.

Results: The zone of growth inhibition round the antibiotic disk increased from 0.6 to 2.34±0.3 mm in all cases of Pseudomonas aeruginosa strain culture. There were no growth changes in control cultures.

Conclusion: The treatment of resistant strains of Pseudomonas aeruginosa with “therapeutic concentration” of dissolved ozone results in antibiotic sensitivity restoration.

P2536 Influence of antibiotic resistance of pseudomonas aeruginosa on presenting features of community-acquired lower respiratory tract infections
Pavliņa Nikolova1, Yavor Ivanov2, Plamen Pavlov3, Tsvan Popova4, Elena Borissova5, Petkana Hristova5.
1Pulmonary Clinic, Medical University, Pleven, Bulgaria; 2Clinic of Internal Diseases, Medical University, Pleven, Bulgaria; 3Department of Social and Preventive Medicine, Medical University, Pleven, Bulgaria

Aim: To evaluate the influence of resistant isolates of Pseudomonas aeruginosa on presenting features for patients with community-acquired lower respiratory tract infections (LRTIs).

Methods: 95 hospitalized patients (67 men, 28 women, average age 66.7±10.9y)
with community acquired pneumonia (CAP), bronchiectasis and exacerbations of chronic obstructive pulmonary disease (COPD) and *P. aeruginosa* isolates were studied during a 5-year period. They were divided into two groups: with susceptible isolates, (n=70, 73.7%, S group) and resistant to antibiotic testing, (n=25, 26.3%, R group) and compared by sex, age, diagnosis, concomitant diseases, treatment, length of stay, outcome.

**Results:** 18% of the patients had CAP, 46.3% - bronchiectasis and 40% - COPD. Most of them had concomitant diseases - ischaemic heart disease: S/R - 62.4%/62.6% resp., diabetes - S/R -11%/12% resp. We found differences in: the change of antibiotic treatment according to the microbiological results (8%/56%/R, p < 0.001); length of hospital stay >15 days - 3%/12% respectively, p < 0.05. Complications of the essential disease were more in the R group (2%/6%/R). The outcome was similar in both groups.

**Conclusions:** The clinical features found in patients with resistant isolates of *P. aeruginosa* compared to susceptible ones were: more complications of the main disease, more frequent change of antibiotics during the course of treatment according to the microbiological results and longer length of stay.

### P2537

**Nebulized antibiotics in patients with non-cystic fibrosis bronchiectasis and chronic pseudomonas aeruginosa infection**

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1 Respiratory Medicine, Hospital de Fuenlabrada, Fuenlabrada, Madrid, Spain; 2 Internal Medicine, Hospital de Fuenlabrada, Fuenlabrada, Madrid, Spain.

**Methods:** Retrospective review of patients with bronchiectasis with *Pseudomonas aeruginosa* (PA) isolated from sputum at least twice during the year prior to nebulized antibiotic (NA) onset and a minimum 6-month follow-up.

**Results:** 17 patients included (9 men), median age 69.7 yrs., average follow-up 753 days (183-1824). Nine patients received more than 1 NA during follow-up (31 NA courses in total): 16 colistin, 14 tobramycin, 1 gentamicin. Average treatment duration: 492.5 days (100-971). Subjective improvement was referred by 12 patients (70.5%). Eradication of PA was achieved in 7 (41.2%), but 1 relapse occurred. 8 patients presented side effects at any time during NA (47%), mainly bronchospasm. Table 1 shows a reduction in mean number of admissions/year and mean days of admission/year for all patients. A statistically significant reduction is observed when NA was eradicated.

### Table 1

<table>
<thead>
<tr>
<th>Period prior to NA*</th>
<th>Period after NA*</th>
<th>Difference between periods**</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=17)</td>
<td>Admissions/year</td>
<td>2.24 (2.17) 1.5 (1.53) 0.73 (0.97)</td>
</tr>
<tr>
<td>Days in hospital/year</td>
<td>31.35 (19.11) 15.68 (17.73)</td>
<td>14.7 (8-36)</td>
</tr>
<tr>
<td>Patients with PA eradication (n=6)</td>
<td>Admissions/year</td>
<td>3.167 (1.27)</td>
</tr>
<tr>
<td>Days in hospital/year</td>
<td>51.67 (54.4)</td>
<td>10.64 (12)</td>
</tr>
</tbody>
</table>

Results expressed as mean and SD (*) or CI 95% (**). ***Within subjects paired T-test for comparing means.

**Conclusions:** 1. NA resulted in clinical improvement in 70.5% of cases and in eradication of PA in 41.2%. Side effects were observed in 47% of cases. 2. NA courses in total): 16 colistin, 14 tobramycin, 1 gentamicin. Average treatment duration: 492.5 days (100-971). Subjective improvement was referred by 12 patients (70.5%). Eradication of PA was achieved in 7 (41.2%), but 1 relapse occurred. 8 patients presented side effects at any time during NA (47%), mainly bronchospasm. Table 1 shows a reduction in mean number of admissions/year and mean days of admission/year for all patients. A statistically significant reduction is observed when NA was eradicated.

### P2538

Mannose binding lectin deficiency is associated with disease severity in patients with non-cystic fibrosis bronchiectasis

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1MRC Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh, United Kingdom; 2Scottish National Blood Transfusion Service, NHS Lothian, Edinburgh, United Kingdom; 3Department of Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; 4Cystic Fibrosis Laboratory, University of Edinburgh, Edinburgh, United Kingdom.

**Background:** Mannose binding lectin (MBL) is a serum protein involved in phagocytic clearance of bacteria, viruses and apoptotic cells. Deficiency of mannose binding lectin is associated with disease severity in cystic fibrosis bronchiectasis but has not been studied in adult non-cystic fibrosis bronchiectasis.

**Methods:** 470 patients with adult non-cystic fibrosis bronchiectasis (confirmed by HCRT) and matched controls were recruited. MBL serum levels were measured by ELISA. MBL deficiency was defined as a serum level < 0.5 μg/ml. Quantitative microscopy was performed on spontaneous sputum samples to determine bacterial load - expressed as Log10 colony forming units/ml (cfu/ml).

**Results:** MBL deficiency was not more frequent in bronchiectasis patients than controls (27.2% vs 29.6%, p=0.4). MBL deficient patients had more severe disease as defined by SABA (19.6% vs. 13%, p<0.001). They suffered more frequent exacerbations (mean 2.8/year vs. 1.4/year, p<0.001) and were more frequently hospitalised for severe exacerbations (31.3% hospitalised vs. 18.1% hospitalised during follow-up). MBL deficient patients more frequently met the criteria for chronic colonisation (70.3% vs. 51.5%, p<0.002). Among those colonised, MBL deficient patients, (n=33) had a higher airflow bacterial load (7.2 vs 3.1 cfu/ml vs 6.37 cfu/ml, p=0.001). MBL deficient patients were also more frequently colonised with *P. aeruginosa* (22.7% vs. 12.3%, p=0.005).

**Conclusion:** Mannose binding lectin deficiency is associated with more severe disease in patients with non-cystic fibrosis bronchiectasis.

### P2539

Effects of subinhibitory concentrations of antibiotics on the biofilm formation of *Pseudomonas aeruginosa*

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**Objective:** To study the effects of the subinhibitory concentrations of four antibiotics on the biofilm formation of *P. aeruginosa*.

**Methods:** 2 types of culture media of 1-broth (LB) and Mueller-Hinton broth (2 Schab) were used with the application of static biofilms model of *P. aeruginosa*.

**Results:** (1) The results of the static-made biofilm were as follows: in the MHB media, azithromycin could induce the biofilm formation of PAO1 when the concentrations were more than 16μg/ml, but inhibited the biofilm formation when the concentrations were less than 8μg/ml. When the PAO1 was cultured in LB, azithromycin would induce the biofilm formation at the sub-MIC concentrations. Ciprofloxacin and ceftazidime could inhibit the biofilm formation at the sub-MIC concentration. Amikacin could induce biofilm formation at the concentration of 0.125 and 0.25μg/ml cultured in MHB and LB respectively. All the results above had statistical difference compared with the blank. The Furazone C-30 was added in the static biofilm model with the azithromycin concentration 8ug/ml and 4ug/ml, the results had no statistical difference. (3) Silver staining results: when the concentration of azithromycin was 8ug/ml the formation of the biofilm was the same as the blank. Under the concentration of silver staining 4 ug/ml, the formation of the biofilm was weaker than the 8 ug/ml. When the PAO1 was cultured in LB, amikacin could induce the biofilm formation at the concentration of 0.125μg/ml and 0.25μg/ml.

**Conclusion:** The sensitivity of the azithromycin to the POAI was different with changing of the environment. Azithromycin could induce the biofilm formation at the subinhibitory concentration. Ciprofloxacin and cefazidime could inhibit the biofilm formation; amikacin could induce the biofilm formation at the concentration of 0.125μg/ml and 0.25μg/ml.
Conclusion: The concept of blocking activity in the serum of patients with non-CF bronchiectasis may provide some explanation for the mechanism of establishment of PA colonisation in the airways of some patients and requires further investigation.

P2541
Sputum neutrophils are related to functional status in non-cystic fibrosis bronchiectasis in subjects in airway colonization

Federico L. Dent, Laura Malagrinò, Francesco Costa, Lorenzo Melisviti, Antonella Di Franco, Maria Laura Bartoli, Cristina Ferretti, Mariella De Santis, Elena Bacci, Pier Luigi Piggiaro. Cardio-Thoracic Department, Respiratory Pathophysiology Section, Pisa, Italy

In 42 subjects with bronchiectasis (13 male, mean age 62.4 ± 9.3 years, 9 ex and 1 current smoker), functional status and airway inflammation were measured. All subjects showed diffuse bronchiectasis (exacerbations in 3 subjects), pulmonary consolidations in 30, and peri-bronchiectasis edusations in 29 subjects. Bronchiectasis was idiopathic in 22, post-infectious in 15, post-TB in 5 subjects. Bacterial airway colonization was demonstrated in 20 out of 32 subjects collecting sputum (8 Pseudomonas, 2 NTMB, 5 Proteus/E.coli, 4 Staphilococcus, 1 Hemophilus infl., 1 Streptococcus). Obstructive syndrome was found in 28 subjects, restrictive syndrome in 2, and normal spirometry in 12. Hypertonic saline-induced sputum was collected in 36 subjects: 29 showed increased neutrophil% (median 79.9%), while 5 subjects showed increased eosinophil%. All except 5 out of 34 subjects showed normal values in exhaled nitric oxide (17.5 ± 16.1 ppb). Significant correlations were found between sputum neutrophil% and FEV1% pred, FEV1/VC% pred, and RV% pred.

In conclusion, significant relationships between sputum neutrophils, and functional findings were found in patients with bronchiectasis and bacterial airway colonization, suggesting that the last one has a role in pulmonary function impairment.

Correlation between Sputum Neutrophil % and functional findings (r, p)

<table>
<thead>
<tr>
<th>FEV1 % pred</th>
<th>FEV1/VC % pred</th>
<th>VR % pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>-0.64, &lt;0.0001</td>
<td>-0.54, 0.0006</td>
</tr>
<tr>
<td>Airway colonization</td>
<td>-0.66, 0.001</td>
<td>-0.48, 0.03</td>
</tr>
<tr>
<td>No airway colonization</td>
<td>-0.40, n.s.</td>
<td>-0.39, n.s.</td>
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</table>

P2542
Survey of microbiology, pseudomonas eradication and antimicrobial prophylaxis in adult patients with non-cystic fibrosis bronchiectasis

Rahul Bhatnagar, Nicholas Withers. Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, United Kingdom

Introduction: Recent guidelines on non-CF bronchiectasis advocate the use of prophylactic antibiotics in frequent exacerbators, and eradication of Pseudomonas Aeruginosa (PA) on first isolation in sputum. We examined the sputum microbiology and antimicrobial treatment in a cross-section of patients seen within our respiratory service.

Methods: Data was collected on all patients seen for routine follow up of non-CF Bronchiectasis for 4 months. We analysed PA status; Prior attempts at eradication of PA; The use of prophylactic antibiotics; and sputum microbiology for the preceding 5 years.

Results: 210 patients were included. The commonest bacterial isolate over the 5 years, other than PA (36%), was Haemophilus influenzae (27%). 48 had positive cultures for PA in the previous 12 months. 40 patients grew PA for more than one year’s duration. Eradication had been attempted in 62% of the patients who grew PA. Regimens included Ciprofloxacin (28%), nebulised colomycin (23%) and a combination of both (20%). 78 (37%) patients were on prophylactic antibiotics, with thrice weekly Azithromycin being used in 61 patients. 47% had been positive for PA at some point. Data for annual exacerbation rates was not available.

Conclusions: PA was cultured in just over a third of patients, with approximately two thirds of these having undergone some attempt at PA eradication using methods in line with recently published guidelines. Only 38% of those remained clear of PA for more than one year afterwards. Approximately 50% of patients on prophylactic antibiotics had no recent isolation of PA, although exacerbation rate data was not included in this survey.

P2543
Inhaled antibiotic treatment. Tolerance, compliance and quality of life

Antonio Alvarez1, Laura Ruano1, Montserrat Vendrell2, Rosa Giron2, Mª Pilar Ausin3, Miguel Angel Martínez2, Marina Blanco5, David de la Rosa1, David Blanquer4, Inês Herreto3, Javier de Gracia1. 1Pneumology Department, Hospital de Reina Sofia. Valencia, Spain; 2Pneumology Department, Hospital Universitari Dr Josep Trueta, Girona, Spain; 3Pneumology Department, Hospital Universitario de la Princesa, Madrid, Spain; 4Pneumology Department, Hospital de Manacor, Manacor, Mallorca, Spain; 5Pneumology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain

Method: Adults attending a bronchiectasis clinic from Dec 2010-Jan 2011 were screened. Spirometry was performed & GOLD criteria for COPD were used to categorise AO. Functional ability was assessed using the MRC dyspnoea (MRCD) scale. The Hospital Anxiety and Depression Scale (HADS) was used to screen for anxiety and depression. A score of ≥8 in either sub-scale (HADS-A, HADS-D) was deemed clinically significant.

Results: N=52 (34F, 18M). Mean age: 61 (SD 13.4). 30 patients (57.7%) had evidence of AO. 6 patients (20%) had mild AO, 11 patients (37%) had moderate AO, 11 patients (37%) had severe AO and 2 patients (6%) had very severe AO. 27 patients (48%) had a HRCD score of ≥3. 30 patients (42.3%) had a HADS-A score of ≥8. 19 patients (28.8%) had both HADS-A and D scores of ≥8. Chi-square analysis showed significant association of clinically significant HADS-A (p ≤ 0.001) and HADS-D (p = 0.013) scores with a HRCD score of ≥3. There was no significant correlation between FEV1 % predicted and HADS-A or HADS-D scores (p=0.98). Scores on HADS were higher in those with active symptoms of AO.

Discussion: Inhaled antibiotics are a convenient option for the treatment of non-CF bronchiectasis. Tolerance, compliance and quality of life of patients with these symptoms are not as poor as expected. Further studies are needed in this population.

P2544
Azithromycin, a novel maintenance therapy in patients with chronic non-CF suppurative lung disease

Simon Twite, Paul Stockton, Sanjeev Agarwal. Respiratory Medicine, St. Helens and Knowsley NHS Trust, Liverpool, Merseyside, United Kingdom

Patients with bronchiectasis experience lower respiratory tract infections with decline in quality of life. The British Thoracic Society statement indicates that macrolides may have disease-modifying activity. A definite recommendation for use is not made in non-CF bronchiectasis. We present experience of Azithromycin in non-CF bronchiectasis as well as other respiratory diseases at a large district general teaching hospital.

In 137 patients were identified on maintenance Azithromycin therapy during a 12 month period. 66% received Azithromycin 250mg daily. Azithromycin provided a significant improvement in the mean time between exacerbations/rescue antibiotics, in patients with non-CF bronchiectasis as well as other lung conditions. The mean time to exacerbation was 64 days, without Azithromycin (range 30-360 days) versus 304.5 days, with Azithromycin (range 14-582 days). 48 patients required rescue antibiotics. Where Azithromycin was electively withdrawn, the patients experienced another exacerbation within 3 months, clinically worsened. This strategy is therefore not recommended. Treatment failure due to side effects only occurred in those patients on a 500mg three times weekly regime. Discussion in the literature raised concerns with atypical mycobacteria, potential for increased colonisation rates and drug resistance. No such concerns were seen in this series. In this series, Azithromycin provided clinical improvement in patients with other non-CF lung disease processes but further studies are needed in this population.

The recommended regime from this study, in those patients with non-CF bronchiectasis is Azithromycin 250mg PO daily.

P2545
Airflow obstruction, functional disability and psychological dysfunction in bronchiectasis

Graham Miller, Helmy Haja Mydin, Anthony De Soya. Cardiothoracic Department, Freeman Hospital, Newcastle upon Tyne, United Kingdom

Introduction: The impact of airflow obstruction, functional disability and psychological dysfunction has previously been described in COPD but not in bronchiectasis. We hypothesised that anxiety and depression may be commoner in bronchiectasis patients with poor functional capacity or evidence of airflow obstruction (AO). Methods: Adults attending a bronchiectasis clinic from Dec 2010-Jan 2011 were screened. Spirometry was performed & GOLD criteria for COPD were used to categorise AO. Functional ability was assessed using the MRC dyspnoea (MRCD) scale. The Hospital Anxiety and Depression Scale (HADS) was used to screen for anxiety and depression. A score of ≥8 in either sub-scale (HADS-A, HADS-D) was deemed clinically significant.

Results: N=52 (34F, 18M). Mean age: 61 (SD 13.4). 30 patients (57.7%) had evidence of AO. 6 patients (20%) had mild AO, 11 patients (37%) had moderate AO, 11 patients (37%) had severe AO and 2 patients (6%) had very severe AO. 27 patients (48%) had a HRCD score of ≥3. 30 patients (42.3%) had a HADS-A score of ≥8. 19 patients (28.8%) had both HADS-A and D scores of ≥8. Chi-square analysis showed significant association of clinically significant HADS-A (p ≤ 0.001) and HADS-D (p = 0.013) scores with a HRCD score of ≥3. There was no significant correlation between FEV1 % predicted and HADS-A or HADS-D scores (p=0.98). Scores on HADS were higher in those with active symptoms of AO.

Discussion: Many patients had severe or very severe airflow obstruction. 50% of...
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P2546
Staphylococcus aureus sensitivity changes to antibiotics under the influence of dissolved ozone
Igor Belyanin, Lubov Selina, Evgeniy Shmelev, Alla Plotnikova. Microbiology, Central TB Research Institute, Moscow, Russian Federation Microbiology, Central TB Research Institute, Moscow, Russian Federation Microbiology, Central TB Research Institute, Moscow, Russian Federation

Aim: To study the sensitivity change of the clinical strains of staphylococcus aureus to antibiotics under the influence of dissolved ozone. (pO3).

Methods: We investigated 20 S.aureus strains from sputum culture resistant antibiotics. A suspension was prepared from a day portion of the agar culture of each strain (1-2 x 10^8/ml), which was treated with dissolved ozone (pO3 3mg/ml) or with air (control) during 5-10-15 min. Then, the strains treated with pO3 were cultured on Muller-Hinton agar containing strains resistant antibiotics and incubated by 370C. In a day of incubation we recorded the results of antibiotic resistance change according the diameter zone of the growth inhibition round the antibiotic discs.

Results: The growth inhibition zone increased from 3.8 to 25.7±2.1 mm in all cases of cultured S.aureus strains treated with pO3. And in cases with control strains the growth inhibition zone was not change.

Conclusion: Staphylococcus aureus sensitivity to antibiotics restores after dissolved ozone treatment.

P2547
Identification of four different metallo-β-lactamases, IMP-1, IMP-7, IMP-19 and VIM-2, in Japanese general hospitals
Naohiro Shibata, Hiroyuki Ohbayashi. Department of Allergy and Respiratory Medicine, Tohno-Kousei Hospital, Mizunami, Japan

Background: Metallo-β-lactamases (MBLs) are bacterial enzymes that hydrolyze β-lactams. MBL-producing gram-negative bacilli have been emerging worldwide. In this study, different MBLs were identified in various lung diseases in the japanese clinical hospitals.

Methods: From Jan. 2009 to Dec. 2010, 1618 GNB strains were submitted to the laboratory of 6 general hospitals in Aichi prefecture. Strains demonstrating a high β-lactamase activity were selected. Preparations of whole cells or cultures were subjected to a screening test for MBL production by using disks containing an MBL inhibitor, sodium mercaptoacetic acid (SMA). PCR and sequencing analyses were performed to confirm the types of MBLs and integrases using primers specific for each gene.

Results: Forty-five patients responded voluntarily to the questionnaires, 35 women, with a mean age of 66.46 (14.6) years. 16 were chronically colonized, with 12 cases of Pseudomonas aeruginosa 42.5% of patients (30% mild depression, 12.5% moderate) had depression. 65% of patients had scores above the 50th percentile in both trait anxiety and in anxiety state. State anxiety and trait anxiety were associated with bacterial colonization (p=0.005 and p= 0.0113) and more specifically to the colonization by Pseudomonas aeruginosa (p= 0.007 and p= 0.029).

Conclusions: Patients with bronchiectasis showed a high percentage of anxiety, both state and trait, as well as depression, although most of this is mild. The chronically colonized patients have higher levels of anxiety in these two aspects.

P2549
Microbiological pattern in infective episodes of bronchiectasis
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Background: Infections usually cause inflammatory reaction and destruction of bronchial wall, this further leads to more disturbance in local defense and a vicious cycle of inflammation and bacterial colonization occurs.

Objectives: The purpose of this paper was to studying the microbiological pattern during infective episodes of Bronchiectasis and possible relation between the invasive Bacteria and lung functions.

Materials and methods: A retrospective analysis of 60 episodes in 50 patients. Fortyeight patients fulfilled our protocol criteria of reliable microbiological result and reproducible lung function tests. The patients were categorized into three stages of severity. Fibroscopic bronchoscopy was performed just after sampling. Sputum sampling was achieved. Cut off point of 1000CFU was considered for positivity of culture media.

Results: H.influenza was the causative agent in 10 episodes (17%), S pneumoniae in 8 (14%) and Paeroginosa in 9 (14%), Morexella catarrhalis in 7 (12%) episodes. Lung function tests revealed an FEV1 with 50% of predicted value in 20 patients (stage 1), an FEV1 with 35-50% in 12 patients (stage 2 and FEV1 with 35% in 8 patients (stage 3).

There was a correlation between deterioration of lung function and the bacteria isolated from patients with infective exacerbations of Bronchiectasis, in acute episodes Pseudomonas Aeruginosa and Enterobactereae were the predominant bacteria in patients with FEV1 at 35% of predicted value.

Conclusion: There were no correlations between the isolated bacteria and the duration of symptoms, number of previous hospitalization, or radiological findings.

In contrast there was a correlation between the deterioration of lung function and the isolated bacteria.

P2550
The role of viruses and other atypical bacteria in bronchiectasis’ exacerbations
Evangelos Balis1, Eugenios Metaxas2, Despina Chrysovergi2, Josip Paparakaskeus2, Nikolaos Spanakis2, George Tatsi2, Athanasios Tisikas3. Pulmonary, Evangelismos General Hospital, Athens, Greece; 23rd Internal Medicine, Evangelismos General Hospital, Athens, Greece; 3Microbiology, Medical School of Kaposvár University, Athens, Greece

Introduction: Exacerbations in patients with bronchiectasis, is thought to occur either because of change in the bacterial load of an existing bacteria or because of colonization with a new bacterial strain. Despite the existence of data for the role of viruses and atypical bacteria in patients with COPD, there is paucity of data about their role in bronchiectasis.

Aims and objectives: To study the effect of atypical bacteria and viruses in bronchiectasis exacerbations

Methods: An observational study was performed. For 12 months, 33 patients with bronchiectasis were followed up in 4 months intervals. They were submitted to bronchoscopy in an effort to determine baseline bacteria. Bronchoscropy was also performed during exacerbations. Real time polymerase chain reaction (PCR) was performed in bronchovascular lavage (BAL) samples for the detection of Chlamydo-philum pneumoniae, Mycoplasma pneumoniae and Respiratory syncytial virus (RSV). In addition, antibody titers against Influenza A, Influenza B, Adenovirus, C pneumoniae and M. pneumoniae were measured.

Results: In total 116 visits were performed (97 baseline and 19 exacerbations). After the first 30 PCR tests, because of cost restrictions, PCR was agreed to be performed only in cases of elevated IgG, seroconversion, or positive IgM titters. Totally 74 PCR tests were performed. RSV was isolated in 4 subjects during baseline periods and none during exacerbations. All PCR tests were negative for atypical bacteria. There was no detection of IgM antibodies against the aforementioned microorganisms.

Conclusions: Despite the small number of recorded exacerbations, atypical bacteria and viruses do not seem to have a role in exacerbations in patients with bronchiectasis.

P2551
Anxiety and depression in patients with bronchiectasis related to bacterial colonization
Gilda Fernandes1, Cristina Martin-Carbajo2, Rosa Girén3, Emma Vasquez1, Rosa Gómez-Punter1, Carolina Cisneros1, Lourdes Ramos2. 1Pulmonary, Evaggelismos General Hospital, Athens, Greece; 23rd Internal Medicine, Evangelismos General Hospital, Athens, Greece; 3Microbiology, Medical School of Kaposvár University, Athens, Greece

Conclusions: In this study, different MBLs were identified in various lung diseases in the japanese clinical hospitals.

Methods: The purpose of this paper was to studying the microbiological pattern during infective episodes of Bronchiectasis and possible relation between the invasive Bacteria and lung functions.

Materials and methods: A retrospective analysis of 60 episodes in 50 patients. Forty-eight patients fulfilled our protocol criteria of reliable microbiological result and reproducible lung function tests. The patients were categorized into three stages of severity. Fibroscopic bronchoscopy was performed just after sampling. Sputum sampling was achieved. Cut off point of 1000CFU was considered for positivity of culture media.

Results: H.influenza was the causative agent in 10 episodes (17%), S pneumoniae in 8 (14%) and Paeroginosa in 9 (14%), Morexella catarrhalis in 7 (12%) episodes. Lung function tests revealed an FEV1 with 50% of predicted value in 20 patients (stage 1), an FEV1 with 35-50% in 12 patients (stage 2 and FEV1 with 35% in 8 patients (stage 3).

There was a correlation between deterioration of lung function and the bacteria isolated from patients with infective exacerbations of Bronchiectasis, in acute episodes Pseudomonas Aeruginosa and Enterobactereae were the predominant bacteria in patients with FEV1 at 35% of predicted value.

Conclusion: There were no correlations between the isolated bacteria and the duration of symptoms, number of previous hospitalization, or radiological findings.

In contrast there was a correlation between the deterioration of lung function and the isolated bacteria.

Aims and objectives: To study the effect of atypical bacteria and viruses in bronchiectasis exacerbations

Methods: An observational study was performed. For 12 months, 33 patients with bronchiectasis were followed up in 4 months intervals. They were submitted to bronchoscopy in an effort to determine baseline bacteria. Bronchoscropy was also performed during exacerbations. Real time polymerase chain reaction (PCR) was performed in bronchovascular lavage (BAL) samples for the detection of Chlamydo-philum pneumoniae, Mycoplasma pneumoniae and Respiratory syncytial virus (RSV). In addition, antibody titers against Influenza A, Influenza B, Adenovirus, C pneumoniae and M. pneumoniae were measured.

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Conclusions: Despite the small number of recorded exacerbations, atypical bacteria and viruses do not seem to have a role in exacerbations in patients with bronchiectasis.
275. Antimicrobial treatment and resistance in lower respiratory tract infections

P2551 Late-breaking abstract: When is pleural fluid microbiology useful?
Kerry Woolnough, Imran Hussain. Respiratory Medicine, University Hospitals of North Staffordshire, Stoke-on-Trent, United Kingdom

Introduction: It is routine clinical practice, and recommended by the British Thoracic Society, that fluid is sent for culture following diagnostic thoracocentesis. Few studies have evaluated the yield from sending all pleural fluid specimens for culture in day to day practice. Culture yield has, however, been studied in cohorts of patients where pleural infection is suspected - with a sensitivity of 54%. We wished to ascertain what our yield is from pleural fluid culture when used as part of a routine workup for an undiagnosed pleural effusion and whether positive cultures were associated with raised inflammatory markers (WCC and CRP).

Methods: We retrospectively analysed all pleural fluid samples sent for culture over the previous 12 months. All specimens were cultured for aerobic and anaerobic bacteria, fungi and mycobacterium. Pleural fluid protein, LDH content, serum CRP and WCC were also recorded.

Results: 485 samples were sent for culture over the 12 month period. There were 42 (8.7%) positive cultures, of which 4 were excluded as contaminants. 20 different organisms were isolated. Streptococcus anginosus and Mycobacterium tuberculosis were the most common. 47% of these positive samples were exudates, non-serous transudates. The remainder of these specimens (53%) had no pleural fluid biochemistry performed. We found a positive yield of 7.8% out of the 485 pleural fluid samples studied. A clear association was found between yield and a raised CRP and WCC with a raised CRP found in 97% of cultures and an increased WCC in 75%.

Conclusions: Routine culture of pleural fluid is neither cost-effective nor clinically useful and should only be requested when pleural infection is suspected, both clinically and biochemically.

P2552 Late-breaking abstract: Inhaled calcium based dry powder inhibits rhinovirus-induced inflammation and exacerbation in a mouse model of allergic airway inflammation
Paul McEvoy2,3,4, Tim Brogan, Stephen Arnold, Pamela Okerholm, Faith Saia, Robert Clarke, David Hava. Research, Palmtrix Inc, Lexington, MA, United States

Acute exacerbations (AE) in asthma are associated with rhinovirus (Rv) infection. AE’s drive disease progression and cause loss of lung function, yet no current therapies target this infectious component. Calcium (Ca) based dry powder (DP) formulations were developed as host-targeted therapies that broadly reduce viral infection in vitro, including Rv. Here, a lead Ca-based DP (PUR118) was tested for efficacy against Rv in a mouse model of infection and AE using Rv1B infection in naive and ovalbumin (OVA)-challenged mice (Bartlett NW et al Nat Med 2008). Mice (Balb/c) were treated with PUR118 or control DP by whole body immersion (IBD) before nasal Rv infection. Bronchoalveolar lavage (BAL) inflammation was evaluated 24h post-infection. Additional indices of infection and exacerbation included: viral titers, and expression of relevant cytokines and chemokines. Rv infection caused significant neutrophilic inflammation in naive mice (7.5 × 10⁵ BAL neutrophils/ml) and exacerbated inflammation in OVA challenged mice (44% increase over control) with increased neutrophils, cytokines and chemokines. In naive mice, PUR118 treatment reduced neutrophilic inflammation by 38%, which correlated with reduced cytokine and chemokine expression. Similar results were observed in OVA mice where PUR118 treatment reduced neutrophilic inflammation by 40%. The data show Ca-based DP significantly inhibits Rv-induced airway inflammation and Rv-driven exacerbation responses in an asthma-like mouse model. These data support the development of inhaled Ca-based DP to treat infectious causes of AE’s in respiratory disease.

P2553 Late-breaking abstract: Prevalence of influenza A H1N1 virus infection in patients with asthmatic crisis of the National Institute of Respiratory Diseases (in Mexico City)
Olivia Sánchez Cabral, Jair Rodríguez Barragán, Manuel de Jesús Castillo López. Respiratory Emergency Department, Instituto Nacional de Enfermedades Respiratorias, Mexico, Distrito Federal, Mexico

Introduction: Among the key precipitating factors of these crises are respiratory infections, mainly viral. In April of 2009, Mexico experienced a new influenza A H1N1 epidemic.

Objective: Determine the prevalence of influenza A H1N1 infection in patients with secondary asthmatic crisis.

Research methods. A transversal research on 5-75 year-old patients was developed between September 1, 2009 and May 17, 2010. Research subjects were admitted to the emergency room with a probable diagnosis of influenza A H1N1 infection and asthmatic crisis. Real-time polymerase chain reaction technique was used to confirm influenza A H1N1.

Findings: We found a global prevalence of 3.6% (195/526) of influenza A H1N1 among the patients that were admitted to the emergency room due to asthmatic crisis. From reviewing medical files we found 124 cases of asthmatic crisis among those patients with a clinical suspicion of influenza A H1N1. The prevalence of the A H1N1 virus among patients with asthmatic crisis was 13.7%. The average age of patients in the study was 35.8 years (mean ± 14.0 years), 71.8% of the patients were women. The average stay in the hospital was 6.9 days, 91% (104/124) of the crises ranged from acute to almost fatal.

Conclusion: Prevalence is relatively high. They can expect an aggravation of the crisis and a longer stay in the hospital.
P2556 Prior outpatient antibiotic use in patients with community acquired pneumonia (CAP) admitted in hospital
Cristina Dei1,2, Filipa Cunha1,2, Andrea Candal1,2, Angelita Nabu3,4,5, Francisco Santos3,4,5, Maria da Carne Aguiar3,4,5, 1Pneumology, Hospital Universitario de Alcorcón, Madrid, Spain; 2Internal Medicine, Hospital Universitario de Alcorcón, Madrid, Spain; 3Pneumology, Hospital Peset, Valencia, Spain; 4Pneumology, Hospital Clinico Valencia, Valencia, Spain; 5Pneumology, Hospital General de Valencia, Valencia, Spain; 6Pneumology, Hospital General de Castellón, Castellón, Spain

Aims: To compare clinical, microbiological, severity and outcomes in patients with CAP admitted to hospital who had received or not previous antibiotic treatment. Method: A 12 months prospective multicenter study was performed in Valencia Community, in Spain (mediterranean area). Factors related comorbidity, etiology, severity, outcomes and mortality, were analyzed. Patients were divided in Group A: antibiotic treatment before admission and Group B: no previous antibiotic treatment.

Results: 1313 CAP, 850 men (65%), 295 in group A (22.4%) with previous antibiotics during 4.3±2.8 days. Patients in group A were younger (59±2.0 vs 65±1.8, p < 0.001), and more patients treated like outpatients (13.2% vs 8.8%, p < 0.05) without differences in resistance. When risk factors and comorbidity were analyzed, in group A there were lower proportion of alcohol abuse, heart failure (p < 0.05) and CAP evolution days (7.4±4 vs 5.4±5, p < 0.01), without differences in other factors. In clinical presentation, group A had more fever and cough (p < 0.001), lesser dyspnea, and altered mental status (p < 0.05), with higher PaO2/FiO2 (293±355 vs 231±169, p < 0.05). No differences in radiology patterns between groups or in etiological confirmation were found. Patients in group A had a lower PSI (81.36 vs 92.15±, p < 0.001), lower rate of complications (p < 0.005) as renal failure, shock, mechanical ventilation and ICU admission (p < 0.05), without differences in intrahospital mortality. The length of stay was shorter in group A (9.45 vs 11±10 days, p < 0.001).

Conclusions: Patients with CAP who received antibiotic treatment before admission were younger, required less hospitalization and the CAP had less severity and complications.

P2557 Clinical outcomes of tigecycline in the treatment of critically ill patients with multidrug-resistant Acinetobactor baumannii infection
Jung Ar Shin1, Hyung Jung Kim1, Min Kwang Byun1. Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

Background: Acinetobacter baumannii (A. baumannii) has emerged as a major cause of nosocomial pneumonia and sepsis in seriously ill patients. Multidrug-resistant A. baumannii (MRAB) is increasing in frequency, and the management of A. baumannii infections is consequently difficult. Therefore, tigecycline is considered the drug of choice for MRAB treatment. The aim of our study was to evaluate the microbiological eradication and clinical effectiveness of tigecycline against MRAB in seriously ill patients, including patients with ventilator-associated pneumonia (VAP).

Methods: We conducted a retrospective study including patients with A. baumannii infections that were treated with tigecycline between April 1, 2009 and March 31, 2010. We analyzed 27 patients with tigecycline for MRAB infections.

Results: The mean age of the patients was 66.2 years (44-83 years) and 20 (74.1%) patients were male. The median length of stay was 74.6 days (11-35 days). MRAB was eradicated from the site of infection in 33 cases (85.2%), however only 17 cases (63.0%) showed positive clinical responses. Overall, an inhospital mortality rate of 51.9% was observed and 4 cases of death were attributable to sepsis. The combination therapy group showed better clinical and microbial success rates than the monotherapy group.

Conclusions: We observed successful microbial eradication rates, but clinical success rates were lower than previous studies.

P2558 Randomised controlled trial of sequential intravenous and oral azithromycin compared with intravenous ceftriaxone followed by cefixime both in combination with clarithromycin in hospitalised patients with community-acquired pneumonia
Arash Etemadi1, Parvez Salehi2, Abbas Chenaneh3, Siamak Ahmadi4. 1Internal Medicine Department, Ahvaz Jondishapour Medical University, Ahvaz, Khuzestan, Islamic Republic of Iran; 2Gerontological Medicine, Ahvaz Jondishapour Medical University, Ahvaz, Khuzestan, Islamic Republic of Iran

Background: The objective of the study was to compare the efficacy, safety, and tolerability of Azithromycin (500 mg) intravenously (i.v.) once daily followed by 250 mg orally twice daily for 14 days with Ceftriaxone (2 g) p.i. by infusion twice daily followed by Cefixime (400 mg) twice daily, both in combination with oral clarithromycin (500 mg) twice daily for the same duration in 63 adult patients initially hospitalized with community-acquired pneumonia. All patients assessed both clinically and bacteriologically one month after the end of the treatment. The results showed statistically significant higher clinical (93.4% vs. 85.4%) and bacteriological success rates (93.7% vs. 81.7%) for patients treated with Azithromycin, irrespective of the severity of the pneumonia. The time to resolution of fever was also faster (median time: 2 vs. 3 days) and hospitalization period was approximately 1 day less for patients who received Azithromycin. The treatment was converted to oral therapy immediately after the initial mandatory 3-day period of i.v.administration for a larger proportion of patients in the Azithromycin group than patients in the control group (50.2% vs. 17.8%). There were fewer deaths (3.0% vs. 5.3%) and fewer serious adverse events (16.5% vs. 16.5%) in the Azithromycin group than in the control group. The rates of drug-related adverse events were comparable in both groups. Thus, monotherapy with Azithromycin is superior to combination regimen of ceftriaxone plus clarithromycin, in the treatment of community-acquired pneumonia.

P2559 Effectiveness of once daily meropenem for the treatment of aspiration pneumonia of elderly patients in long-term care facilities
Arash Etemadi1, Parvez Salehi2. 1Internal Medicine Department, Ahvaz Jondishapour Medical University, Ahvaz, Khuzestan, Islamic Republic of Iran; 2Gerontological Medicine, Ahvaz Jondishapour Medical University, Ahvaz, Khuzestan, Islamic Republic of Iran

Objective and background: Aspiration pneumonia is a major health problem in residents of long-term care facilities. Antibiotics with broad coverage against gram negative and anaerobic bacteria, such as carbapenems, are cornerstones of treatment. However, once daily administration of meropenem for ambulatory patients is not routine yet.

Methods: A retrospective study of 31 elderly patients with aspiration pneumonia (17 males, 14 females; mean age 85 years) was conducted. In addition, the efficacy and safety of once daily intravenous meropenem (3g) for the treatment of this condition was evaluated.

Results: The overall detection rate of bacteria was 87% (32% monomicrobial, 55% polymicrobial). gram-negative enteric bacilli and anaerobic bacteria were isolated with the same frequency (20%) The overall clinical efficacy rate of meropenem therapy was 61%. The mortality rate was 10%.

Conclusion: The use of antibiotics effective against anaerobic bacteria may be necessary for patients with potentially fatal aspiration pneumonia. Once daily treatment with Meropenem (3g) for aspiration pneumonia is clinically effective and tolerable in elderly patients.

P2560 Potential protective role of prior to diagnosis antibiotic treatment in community-acquired pneumonia: Clinical presentation and outcomes
Francisco Santos1,2, Estrella Fernandez1,2, Maria Carolina Aguir1,2, Marisa Briones1,2, Eusebi Chiner3, Cristina Senent3, Jose Sancho3, Josè Blanquer4,5. 1Pneumology, Consorci Hospital General Universitaritat, Valencia, Spain; 2Pneumology, Hospital De Peset, Valencia, Spain; 3Pneumology, Hospital Arnau de Vilanova, Valencia, Spain; 4Pneumology, Hospital Clinico Universitari, Valencia, Spain; 5Pneumology, Hospital Clinic Universitari, Valencia, Spain; 6Intensive Care Unit, Hospital Clinic Universitari, Valencia, Spain

Aims: To evaluate the role of prior to diagnosis antibiotic therapy in the clinical presentation of community-acquired pneumonia (CAP) and its influence in the outcomes.

Methods: CAP’s (excluding HCAP) receiving antibiotic treatment before hospital admission were analyzed. We assessed demographic factors, comorbidities, signs, symptoms, and outcomes. Logistic regression analysis was performed to establish causal relationships.

Results: We analyzed 1.197 cases of hospitalized CAP in which 22.6% had a history of prior antibiotic treatment, with a mean duration of 3.9 (2.2) days. Beta-lactams were the most frequently used (52.7%) followed by macrolides (29.2%), and quinolones (18.1%). Multivariate analysis showed that patients who received prior antibiotic treatment showed less pneumonia severity on admission (PSI II 64.7% vs. 59.0%, OR 1.85 95% CI 1.44-2.45) and pneumococcal etiological diagnosis was less frequent (13.3% vs. 21.7%, OR 0.61 95% CI 0.41 to 0.92). In patients receiving prior to diagnosis treatment, a shorter hospital stay (8.3 (1.5) vs. 10.6 (9.7), P = 0.001), lower frequency of respiratory failure (21.2% vs. 28.8%, p = 0.023), septic shock (1.5% vs. 4.2%, p = 0.034) and ICU admission (3.3% vs. 6.8%, p = 0.035) were found. No significant differences in mortality were observed.

Conclusions: 1. Prior to diagnosis antibiotic treatment of CAP has a role in modifying the severity of CAP and an impact on pneumococcal etiologic diagnosis. 2. The use of antibiotics before the diagnosis of pneumonia is associated with a shorter hospital stay and less development of complications in our series.

P2561 Antibiotic prescription patterns in hospitalized patients with community-acquired pneumonia in local hospital: 10 year follow-up
Alexander Vizel1, Galina Lysenko2. 1Phtthiopulmonology, Kazan Medical University, Kazan, Tatarstan, Russian Federation; 2Standardization and Quality, Ministry of Health of Tatarstan Republic, Kazan, Tatarstan Republic, Russian Federation

Background: In Tatarstan Republic (Russia) regularly update the guidelines of an
community-acquired pneumonia (CAP) and spend work on updating of knowledge of doctors: lectures, seminars, publications.

**Objective:** We sought to examine patterns of antibiotic prescription during last 10 years in a local hospital. We have estimated prescription of antibiotics at a pneumonia in 2000 (174 cases), 2005 (321) and 2010 (182 cases).

**Intervention:** chart reviews of 771 individual admissions with the diagnosis of pneumonia between January 2000 and December 2010.

**Results:** Compliance with national guidelines for the treatment of CAP increased within 10 years that the table reflects.

**Most often applied antibiotics at a community-acquired pneumonia**

<table>
<thead>
<tr>
<th>Drug/Year</th>
<th>2000</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>73%</td>
<td>16.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>14.4%</td>
<td>19.0%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Cephalosporin I generation</td>
<td>15.5%</td>
<td>3.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Cephalosporin III generation</td>
<td>4%</td>
<td>58.6%</td>
<td>87.6%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>27%</td>
<td>36.4%</td>
<td>32.0%</td>
</tr>
<tr>
<td>Fluoroquinolones II generation</td>
<td>11.5%</td>
<td>4.7%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Fluoroquinolones III-IV generation</td>
<td>0%</td>
<td>0.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>4.0%</td>
<td>0.6%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Sulfamidines</td>
<td>6.9%</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.6%</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Frequency of application III generation cephalosporins has increased about 4% to 87.6%, respiratory fluoroquinolones - about 0% to 16.7%.

**Conclusion:** Research has shown that prescription of antibiotics changed within 10 years. Appointments in 86.7% of cases corresponded to the recommendations accepted in Russia in 2010.

**P2562 Clinical efficacy of bolus versus continuous-infusion of piperacillin-tazobactam in VAP treatment**

Fukun Fuhimi1,2, Hamid Reza Jamil2, Payam Tabarsi1, Shadi Ban Asadi1, Somayeh Ghafer1, Seyed Mohammad Reza Hashemi1,2, Clinical Pharmacy Department, School of Pharmacy, SBMU, Tehran, Islamic Republic of Iran; 2Critical Care, Chronic Respiratory Disease Research Center CRDRC/NRITLD, Tehran, Islamic Republic of Iran; 3Mycobacteriology Research Center, NRITLD, Tehran, Islamic Republic of Iran; 4Pharmaceutical Care Department, TB and Lung Disease Research Center, NRITLD, Tehran, Islamic Republic of Iran

**Introduction:** VAP is the most frequent intensive care unit (ICU) acquired infection. In an effort to improve the clinical outcome, great attention must be given to early and accurate diagnosis, optimal doses of effective antibiotic and best routes of administration.

**Aims and objectives:** The aim of this study was to evaluate the clinical outcome of piperacillin/tazobactam via continuous infusion by serial measurements of Clinical Pulmonary Infection Score (CPIS), compared to intermittent bolus

**Methods:** This study was designed as a prospective clinical trial of continuous infusion or intermittent bolus of a fixed combination of piperacillin/tazobactam and was conducted at the semi-closed intensive care unit of a university hospital.

**Results:** There were no significant differences in characteristics between the two groups. The mean ± SD age of the patients was 53 ± 8.27 years. The APACHE II score was 20.4 ± 6.1 in the CI group and 18.8 ± 5.9 in the IB group (p=0.319). There was a worsening on day 3 compared with the CPIS on day 1, 8.70 ± 2.13 vs 7.04 ± 1.55, and then CPIS slowed improvement from day 3. In the CI group more tendency for improvement was observed.

**Conclusion:** This study suggests that the real value of our findings will achieve within 10 years that the table reflects.

**P2563 difference of patient background with pneumonia between monotherapy and combination**

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**Introduction:** to select combination therapy of antibiotics.

**Methods:** The current guidelines recommend combination therapy of antimicrobials and Gerontology Hospital from April 2008 to December 2010, and treated with carbapenem (A group, n=70) or combination of carbapenem-sulbactam (B group, n=68).

**Methods:** Information on age, gender, weight, risk factors of PDR pathogens, pneumonia type (CAP/HAP/CF/HAP), Barthel index, clinical response, duration of therapy and 30-day mortality were obtained from chart review. We compared the aforementioned factors between two groups using multiple logistic regression analysis.

**Results:** There were significant differences about the aforementioned factors except age between A and B group in univariate analysis. However, in multivariate logistic regression analysis, only Barthel index was significantly different between both groups (81.8 ± 29.2 in A group vs. 59.1 ± 40.3 in B group, P<0.01, respectively). The clinical efficacy rates were 79% in A and 63% in B groups, respectively. The 30-day mortalities were 13% in A and 38% in B groups, respectively (P=0.067). Duration of antibiotics therapy was significantly shorter in A group compared with B group (7.3 ± 4.7 vs 19.3 ± 8.2 days, respectively, P<0.01).

**Conclusion:** Barthel index was the independent factor which affected physicians to select combination therapy of antibiotics.

**P2564 Auditing patterns of azithromycin use in respiratory disease**

David Hodgson1, Robert Hurford1, Tim Harrison1, Dominick Shaw1, 1Nottingham Respiratory Biomedical Research Unit, University of Nottingham, Nottingham, United Kingdom; 2University of Nottingham Medical School, University of Nottingham, Nottingham, United Kingdom

**Introduction:** In response to increasing use of Azithromycin in respiratory disease we set out to audit local prescribing and clinical outcome.

**Methods:** Data on all Azithromycin prescriptions from a Respiratory Consultant in a large UK teaching hospital between 1st September 2009 and 31st March 2010 were collected. There were 192 prescriptions corresponding to 123 patients. After excluding patients with cystic fibrosis (CF) and Pseudomonas aeruginosa colonisation, 62 sets of notes were reviewed. The subjective clinical benefit of Azithromycin and objective improvement in terms of exacerbations or lung function was assessed.

**Results:** Despite the large variation in phenotypic disease (Figure 1), there was an overall reduction of 0.36 exacerbations per month (P<0.001, 95% CI: 0.27–0.46). On further analysis we found that those with evidence of bronchiectasis were significantly more likely to improve after Azithromycin therapy than those without; 88% and 39% respectively (P<0.001).

**Conclusion:** Azithromycin is used in a variety of respiratory conditions and we found variable recording of its benefit. A more formal assessment of benefit is required, especially in light of its side effect risk and potential for microbial resistance. Additional randomised controlled trials to further guide treatment are recommended.

**P2565 Pev antibody prophylaxis in combination with antibiotic therapy reduces lung injury and improves survival in Pseudomonas aeruginosa infected mice Yuanlin Song1, Mark Baer2, Ramya Sirivongsavan3, Juliana Lima3, Geoffrey Yarranton3, Christopher Bebbington3, Susan Lynch1,1 Department of Pulmonary Medicine, Zhongshan Hospital, Shanghai, China; 2KaloBio Pharmaceutical, Inc., KaloBio Pharmaceutical, Inc., San Francisco, CA, United States; 3Gasterenterology, University of California, San Francisco, San Francisco, CA, United States; 4Anesthesia and Perioperative Care, UCSF, San Francisco, CA, United States

The type III secretion system (TTTS) of Pseudomonas aeruginosa facilitates direct injection of cytotoxins into host cell cytoplasm. PeV, located at the tip of the needle-like injectosome, is an essential component of this virulence system. Mab166, a murine monoclonal antibody against PeV has demonstrated efficacy against P. aeruginosa infection resulting in increased survival and reduced lung injury in a variety of mouse models of infection. We hypothesized that administration of Mab166 prophylactically in combination with conventional antibiotics (administered subsequent to infection) could further improve survival of P. aeruginosa infected mice. Three antibiotics (ciprofloxacin, tobramycin and cefazidime), commonly prescribed for P. aeruginosa infections were used for this study. Consistently, compared to other treatment groups, the combination of Mab166 administered with PeV antibody prophylaxis in combination with antibiotic therapy reduced significantly more likely to improve after Azithromycin therapy than those without; 88% and 39% respectively (P<0.001).

**Conclusions:** Azithromycin is used in a variety of respiratory conditions and we found variable recording of its benefit. A more formal assessment of benefit is required, especially in light of its side effect risk and potential for microbial resistance. Additional randomised controlled trials to further guide treatment are recommended.

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**Conclusions:** Azithromycin is used in a variety of respiratory conditions and we found variable recording of its benefit. A more formal assessment of benefit is required, especially in light of its side effect risk and potential for microbial resistance. Additional randomised controlled trials to further guide treatment are recommended.
A multivariable regression logistic analysis adjusted for immune system status and Age 73 was an independent risk factor for mortality (OR 7.5; CI95%1.75-32). Empiric antibiotic coverage of aetiologic pathogen, showed that MDR infection was found in 28 (3%). Factors that most likely were associated to a MDR infection were a previous hospitalization (odds ratio 5; CI95% 2.11-11.8) and antibiotic treatment (OR 2.48; CI95% 1.086-1.1) within 90 days. MDR infection was associated with a higher mortality (p 0.001), OR 5; CI95% 2.11-11.8 but not with ARF development (p 0.093). Clinical features on admission are listed in table 1.

Table 1. Clinical features on admission

<table>
<thead>
<tr>
<th>Age</th>
<th>PS1</th>
<th>COPD</th>
<th>Immuno-depression</th>
<th>PaO2/FiO2</th>
<th>MDR p</th>
</tr>
</thead>
<tbody>
<tr>
<td>73±14</td>
<td>88±7</td>
<td>11±3</td>
<td>0.0001</td>
<td>265±76</td>
<td>0.030</td>
</tr>
</tbody>
</table>

The prevalence of LTBI was 16.7%. CXRs were needed in 236 subjects. CXRs could have been avoided in the 192 subjects (81%) who had a normal IGRA test. Normal CXRs, within the preceding year, were associated with LTBI (p < 0.05). CXRs could have been avoided in the 192 subjects (81%) who had a negative IGRA test. The 108 that declined CXRs did not report any symptoms of TB, and 105 of them had negative IGRA tests. Normal CXRs, within the preceding year, were associated with LTBI (p < 0.05). CXRs could have been avoided in the 192 subjects (81%) who had a negative IGRA test.

Conclusion: The IGRA test first protocol was more cost-effective than a “CXR first protocol”, during TB screening, due to a reduction in the number of CXRs required. The presence of symptoms, a positive IGRA/Mantoux test, or risk factors for active TB should be indications for a CXR.
P2572 Clinical, epidemiological and evolving profile of miliary tuberculosis: Study of 48 cases
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Miliary tuberculosis is a rare but severe form of TB often due to hematogenous spread of Mycobacterium tuberculosis. It represents less than 2% of tuberculosis in our context. We conducted a retrospective study of 48 cases collected in our Respiratory Diseases department between 2003 and 2010. Female cases were pre-dominant with 60%. The mean age was 35 years old. The history of tuberculosis spread of Mycobacterium tuberculosis. It represents less than 2% of tuberculosis in our context.

Results: Mean age was 43.3 ± (13.8) years; 75.0% were male. Median sputum culture conversion time was 46 days. Delayed sputum culture conversion was found in 27.2% (n=37) of patients. In univariate analysis, unemployment (38.0% vs. 20.9%, p<0.031), HIV positivity (53.3% vs 24.0%, p=0.028), bilateral radiological involvement (42.0% vs 19.0%, p=0.005), cavitory disease (32.6% vs 15.9%, p=0.041), and colony counts ≥ 100 (53.7% vs 8.3%, p=0.018) were risk factors for persistent positive culture. In multivariate logistic regression analysis, only bilateral radiological involvement (odds ratio (OR) 1.7, 95% confidence interval (CI): 1.5-9.0) and higher colony counts (OR 5.8, 95% CI: 1.2-27.4) were independently associated with delayed sputum culture conversion.

Conclusions: Delayed sputum culture conversion was found in approximately one third of patients. Logistic regression analysis determined higher colony counts and independent risk factors for delayed sputum culture conversion.

P2573 Completion of treatment for latent tuberculosis infection
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Background: The effectiveness of latent tuberculosis infection (LTBI) treatment depends largely on adherence.

Aim: To identify factors associated with patients’ completion of treatment for LTBI.

Methods: We reviewed the characteristics of all patients who were prescribed a six month course of treatment with isoniazid for LTBI at the Chest Clinic of a large tertiary hospital between 01/2000 and 04/2008. A supply of isoniazid was dispensed one month at a time by Chest Clinic nurses. Treatment completion was defined as pickup of ≥ 80% of prescribed doses.

Results: During the study period, 143 patients were started on this course of therapy. Their mean (SD) age was 25 (16) years and 43% were male. Seventeen patients were excluded from the analysis because their treatment was interrupted (n=4) or ceased (n=13) by their treating physician. Of the remaining 126 patients, 25 (20%) did not complete treatment. Treatment completion was not significantly related to patients’ sex, age, tuberculosis (TB) incidence in their country of birth, TST conversion status, smoking status, baseline liver function tests, or indication for isoniazid treatment (contrast versus other indications). However, among those who were contacts of a patient with active TB (n=10) those who were not living in the same household as the index case were more likely to fail to complete treatment (relative risk 7.2, 95% CI 2.6 to 20.7).

Conclusions: In this cohort, with monthly supervision of drug collection, 1 in 5 patients who commenced treatment for LTBI did not complete their course of treatment. Non-household contacts of patients with active TB were at an increased risk of not completing treatment. This may prompt researchers to encourage treatment completion.

P2574 Differences between age related clinical presentation of pulmonary tuberculosis (TB)
Ramonona Nedelec, Oana Claudia Deleanu, Diana Pocora, Andra Malanu, Ileana Rohan, Anca Macri, Roxana Nemes, Ruxandra Ulmeana, Florin-Dumitru Mihalasan. Pneumology, Institute of Pneumology “Marius Nasta”, Bucharest, Romania; Pneumology, University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania; Bronchology, Faculty of Medicine and Pharmacy - Oradea University, Bucharest, Romania

Aims: This study aimed to compare clinical features, predisposing factors and imaging findings of pulmonary TB in elderly and young adults and to determine any existing difference between the two groups.

Methods: A total of 179 patients diagnosed with TB were divided into two groups: younger (<65yrs) and older (>65yrs). Mean characteristics (gender, smoking, TB forms, lesion extension and type, symptoms, comorbidities, side effects) were analyzed. Statistical analysis was done using SPSS software (chi-square test and student’s t-test).

Results: There were 102 young adults (mean age 38.97±12.45yrs; 60 men, 42 women) and 77 elderly patients (mean age 73.38±6.42yrs; 50 men, 27 women) with TB. The elderly patients were smokers (61% vs 45% P=0.05), more likely to have dyspnoea (57.14% vs 28.4% P<0.001) and night sweats (63.6% vs 24.5% P=0.011). Young subjects present asymptomatic or anorexia associated forms. Elderly patients frequently showed extensive unilateral infiltration in chest X-rays (19.5% vs 3.9% P<0.001); these lesions were often misdiagnosed as pneumonia (6.5% vs 1% P=0.04). Predisposing factors were more prevalent in elderly subjects who had a significantly higher frequency of diabetes mellitus (14.3% vs 2% P=0.002), ischemic heart disease (18.2% vs 2% P=0.01), congestive heart failure (10.4% vs 1% P=0.04), malignancy (15.5% vs 1% P=0.001), arterial hypertension (61% vs 47% P<0.002) and caxoesia (7.8% vs 1% P=0.02).

Conclusions: In Romania, TB is more frequent in younger people, although older subjects represent a population at high risk to develop sever forms. Diagnosis in elderly patients can be challenging, since they may not display classic signs and symptoms.

P2575 Causes of delay in the diagnosis of pulmonary tuberculosis
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Background: Early diagnosis of tuberculosis and its treatment are essential in a control program, as it reduces the severity, mortality and transmission of the disease in the community.

Aim: To determine the time between symptom onset and demand of health services (patient delay) and between first consultation and start of treatment (health care delay). For each interval, determinants of possible delays were analyzed.

Methods: A cross-sectional study was performed in Porto (North of Portugal), based on data from the national tuberculosis surveillance system, including confirmed cases of pulmonary tuberculosis diagnosed during 2008/2009. We defined 3 weeks for patients’ and 1 week for health cares’ delays as cut off points to dichotomize the sample into either delay or non delay. Chi-square test were used to analyze associations (α=0.05).

Results: We analyzed 165 individuals and of those, 122 (76.5%) were male and the mean age 48 years old. Median patient delay was 4 weeks. Patient delay was more frequently associated (although not statistically significant - p>0.01) with unemployment (68.4% vs 61.4%), alcoholism (76.5% vs 62.7%) and other co-morbidities (72.2% vs 64.9%). The median time of health care delay was 1 week. Negative sputum smear was significantly associated (69.7% vs 34.2% - p=0.001) with this delay.

Conclusion: We could not identify target groups significantly associated with patient delay. Strategies should be directed to general population in order to increase awareness about the disease. Negative sputum smear was associated with health care delay which can be justified by the time needed to study these patients.

P2576 The effect of smoking on the treatment outcome in patients with pulmonary tuberculosis: A prospective cohort study
Myla Castillo, Ma Encarnita Limpin. Division of Pulmonary and Critical Care, Philippine Heart Center, East Avenue, Quezon City, Philippines

Smoking and tuberculosis have great impact on health. Smoking is prevalent worldwide occurring in 20% of adults while tuberculosis is a universal problem. Studies have shown that although smoking has no etiological role in TB, higher prevalence of TB has been observed in smokers. However, only few studies have evaluated the impact of smoking on TB treatment.
Background: Pulmonary tuberculosis (TB) is a chronic disease, with slow evolution and slow recovery with specific treatment. Some of the cases have differential diagnosis doubt over a long period of time.

Material and methods: We present a series of 6 patients (5 females), mean age 43.1 years (range 27-70 years), with various respiratory symptoms and opacities on chest radiography, who needed multiple diagnosis procedures over a long period of time before the diagnosis of TB.

Results: The delay of diagnosis was 19.1 month (range 5-24 months). Symptoms consisted of: cough (6), dyspnea (4), and low grade fever (2). Chest X-ray showed: pulmonary micronodular pattern (4), consolidation (1), and pseudotumor (1). CT scan showed “tree in bag” pattern in patients with micronodules on chest radiography.

One patient monitored several times with CT-scan and bronchoalveolar lavage was diagnosed with TB after 2 years, when cavities appeared on CT-scan and sputum smear was positive for AFB. One patient had diabetes and one had viral C hepatitis. All had fever and poor general condition. One patient presented with acute respiratory failure. Chest x ray revealed bilateral interstitial micronodules in all cases. Tuberculin skin reaction was positive in 3 cases. Three cases were smear positive. Medullary biopsy confirmed TB in 1 case. One case was retrospectively confirmed by good response to treatment. Extrapulmonary localization was: hepatic in 5 cases, splenic in 2 cases, lymph node in 1 case, cerebromeningeal, mediastinal, osteoarticular and renal in 1 case each. Treatment administered urgently was based on anti tubercular treatment and treated urgently as such.

Conclusion: MT is a rare form of TB in BCG vaccinated patients and occurs more frequently in immunocompromised patients. To evaluate frequency and clinical features of MTB in immunocompromised patients, we analyzed all cases of MTB diagnosed in a pulmonary department in 2000 and 2010, in patients with negative HIV test. We study 5 cases with the case of 15 months leading to an incidence of 2.6% among all TB patients seen in the same period. All were male, smokers and BCG vaccinated. One patient had diabetes and one had viral C hepatitis. All had fever and poor general condition. One patient presented with acute respiratory failure. Chest x ray revealed bilateral interstitial micronodules in all cases. Tuberculin skin reaction was positive in 3 cases. Three cases were smear positive. Medullary biopsy confirmed TB in 1 case. One case was retrospectively confirmed by good response to treatment. Extrapulmonary localization was: hepatic in 5 cases, splenic in 2 cases, lymph node in 1 case, cerebromeningeal, mediastinal, osteoarticular and renal in 1 case each. Treatment administered urgently was based on anti tubercular treatment and treated urgently as such.

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ICU mortality of TB patients. Our results can contribute to a better understanding of these nowadays TB phenomena related to long and aggressive chemotherapy, pulmonary co-morbidity, disseminated disease with CNS involvement, previous MDR and XDR of discharging Mycobacterium tuberculosis, HIV co-infection, and to identify the factors that predict ICU mortality.

**Aim:** To study information of different examination methods for lung cancer diagnostics in patients of antituberculosis departments

**Methods:** We analyzed results of medical examinations (clinical, roentgen and bronchological) of 2516 patients in hospital departments of Scientific Practical Centre for Pulmonology and Tuberculosis

**Results:** Incidence rate of bronchologic cancer was 1.7% (43 patients); average patient age was 60.3 years; males – 76.7%, females – 23.3%. 74.4% cases with lung tuberculous were revealed during the patient’s stay in the hospital and only 25.6% (11 patients) during the systematic R-examination. 18 persons had tuberculosis, the rest patients were examined for specific or nonspecific specific. According to medical examinations 33 patients had tumour lung lesion, 10 had combination of lung tuberculosis and cancer. Central cancer was suspected in 44.2% patients and peripheral cancer in 50% during the rauting R-examination. Computed tomography increased diagnoses of central lung cancer to 68.4%. In peripheral cancer data of computed tomography was informative in 7 of 9 patients. Bronchoscopy with lung and bronch biopsy permitted to determine lung cancer in 88.9-100%. We had the most difficulties in lung cancer diagnostics because its combination with active tuberculosis and bacilli shedding.

**Conclusion:** Early diagnostics of lung cancer in antituberculosis departments is possible with availability of timely bronchoscopy and oncologic alert in physicians.

**P2582**

**Diagnosics of lung cancer in antituberculosis departments**

Pavel Kryevans1, Halina Tamashakina2, Dzmitry Kryevans1, 1Pulmonology and Tuberculosis, Belarussian State Medical University, Minsk, Belarus; 2Clinic, Scientific Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus

**Aim:** To study information of different examination methods for lung cancer diagnostics in patients of antituberculosis departments

**Methods:** We analyzed results of medical examinations (clinical, roentgen and bronchological) of 2516 patients in hospital departments of Scientific Practical Centre for Pulmonology and Tuberculosis and in 2006-2012 in the Scientific Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus.

**Results:** Incidence rate of bronchologic cancer was 1.7% (43 patients); average patient age was 60.3 years; males – 76.7%, females – 23.3%. 74.4% cases with lung tuberculous were revealed during the patient’s stay in the hospital and only 25.6% (11 patients) during the systematic R-examination. 18 persons had tuberculosis, the rest patients were examined for specific or nonspecific specific. According to medical examinations 33 patients had tumour lung lesion, 10 had combination of lung tuberculosis and cancer. Central cancer was suspected in 44.2% patients and peripheral cancer in 50% during the rauting R-examination. Computed tomography increased diagnoses of central lung cancer to 68.4%. In peripheral cancer data of computed tomography was informative in 7 of 9 patients. Bronchoscopy with lung and bronch biopsy permitted to determine lung cancer in 88.9-100%. We had the most difficulties in lung cancer diagnostics because its combination with active tuberculosis and bacilli shedding.

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**P2583**

**Intensive care of patients with tuberculosis**

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**Introduction:** Multi and extensively drug resistance (MDR, XDR), HIV association, these nowadays TB phenomena related to long and aggressive chemotheraphy, frequent disease progressions and complications, elective and emergency surgery, lead to increase in intensive care (IC) requirement for TB patients.

**Aim:** The aim of the study was to describe the characteristics of patients with TB requiring IC, to evaluate the risk factors for intensive care unit (ICU) admission, and to identify the factors that predict ICU mortality.

**Patients and methods:** Patients with TB admitted to the National Research and Practical Centre for Pulmonology and TB (Centre) during one year (2010) entered the study. Demographic, clinical, radiological and bacteriological data at hospital admission and during ICU stay were recorded, and risk factors for ICU admission and death were calculated.

**Results:** A total of 200 patients were admitted to the Centre during the study period. 280 of them had MDR-TB, 78 – XDR-TB and 20 – HIV-TB co-infection. 144 TB patients were admitted to ICU, in 43 of them admission was related to surgery. 31 patients died giving 21.5% of ICU mortality rate. Factors significantly related to ICU admission were: previous TB treatment, history of imprisonment, MDR and XDR of discharging Mycobacterium tuberculosis, HIV co-infection, and excessive alcohol use. Risk factors for ICU death were: body mass index, pulmonary co-morbidity, disseminated disease with CNS involvement, previous ICU admission.

**Conclusions:** These data indicate a relatively high requirement in IC as well as high ICU mortality of TB patients. Our results can contribute to a better understanding of characteristics associated with IC and mortality for TB patients.

**P2584**

**Characteristics of patients with pulmonary tuberculosis in intensive care unit**

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**Aim:** To describe the characteristics of patients with tuberculosis (TB) requiring intensive care treatment and to identify the factors affecting mortality.

**Method:** We conducted a retrospective study between 2004 and 2010. The data of 53 TB patients treated in intensive care unit were studied. Demographic, clinical, radiological and bacteriological data, reason for admission to the intensive care unit, APACHE II score, mechanical ventilation, duration of ICU and hospital length of stay, complication of intensive care, treatment and outcome were recorded. Predictors of mortality were assessed Chi-square test was used for statistical analysis.

**Result:** A total of 40 TB patients (7 females, median age 54.5 years) admitted to ICU were included. 25 of them had COPD (50%) and diabetes mellitus (17.5%). The most common symptoms are dyspnea (80%) and cough (62.5%). All of the patients were pulmonary tuberculosis and 82.5% ‘s were new cases. Radiologically, 26 (65%) had widespread pulmonary infiltrates, 4 (7.5%) patients had miliary tuberculosis. 35 (87.5%) of the cases diagnosed with culture positivity. The most common reason for hospitalization in intensive care unit was acute respiratory failure (32 cases), and the median APACHE II score was 22 (17-26). 92.5% of the patients received mechanical ventilation and 30 (75%) of the patients died. There was no significant difference between the studied parameters in patients who have died, and alive (p>0.05).

**Conclusion:** In this study we found a high mortality rate in TB patients requiring intensive care unit.

**P2585**

**Effect of pulmonary arterial hypertension on outcome of pulmonary tuberculosis**

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**Objectives:** Due a growing range of therapeutic options, early diagnosis of pulmonary arterial hypertension may change survival of patients. This study performed to evaluate effect of concomitant pulmonary arterial hypertension on outcome of new cases of pulmonary tuberculosis.

**Methods:** A cross sectional study of 777 new cases of pulmonary tuberculosis were recruited in National Research Institute of Tuberculosis and Lung Disease, Tehran, Iran. Pulmonary arterial hypertension was defined as systolic pulmonary arterial pressure > 30 mmHg estimated by resting transthoracic echocardiography. We assessed the relationship between pulmonary arterial hypertension on admission and survival during six months treatment of tuberculosis.

**Results:** Of 777 new cases of pulmonary tuberculosis, 74 (9.5%) had systolic pulmonary arterial pressure > 30 mmHg. Ten of them (13.5%) died during treatment period in comparison to 5% among cases without pulmonary arterial hypertension (P=0.007). Logistic regression analysis confirmed this association.

**Conclusion:** A significant association was found between mortality and presence of pulmonary arterial hypertension among new cases of pulmonary tuberculosis. Therapeutic intervention may change outcome of these patients.

**P2586**

**Pulmonary tuberculosis with polyneuro-radiculopathy: Not forget Guillain-Barré syndrome!**

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**Background:** Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuro-radiculopathy and known to follow a variety of viral, mycoplasmal, bacterial and chlamydial infections. The association with tuberculosis has been exceptionally reported. We report an unusual case of GBS associated with pulmonary tuberculosis.

**Case report:** An 19-year-old man was admitted to hospital with cough during one month and hemoptysis. Chest X-ray showed multiple ring shadows in both upper zones suggestive of pulmonary tuberculosis. Sputum-smears and culture were positives for mycobacterium tuberculosis. Anti-TB drugs were initiated and they were well tolerated. Twenty one days later, the patient suffered acute and progressive legs weakness that ascended to the arms and face with sensory loss and total areflexia. These clinical, radiological and laboratory investigations were normal. Antibodies to nuclear antigens were negative. Cerebrospinal fluid (CSF) revealed protein 210 mg/dl, sugar 75 mg/dl without cells. Neurophysiological study was consistent with sensitive- motor axonal and radicular neuropathy with denervation. These clinical, radiological and laboratory investigations were conform to description of GBS. Intravenous immunoglobulin therapy (0.4 g/kg over 5 days) and physiotherapy were given, with slow neurological recovery. At review 6 months later, patient had completely recovered.

**Conclusion:** The pathogenesis of GBS in infective disease is by no means clear. Authors suggested that GBS can be resulted from direct invasion of the nerve roots by tuberculosis bacilli.
P2587

Frequency of tuberculosis on bronchial anthracosis, systematic review and meta-analysis

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Introduction: Anthracosis is the black pigment discoloration of bronchi which may cause bronchial obstruction. The objective of this study was to collect the data about the association of tuberculosis and anthracosis of lung by systematic review and meta-analysis.

Materials and methods: All studies that had enough information about frequency of tuberculosis in anthracosis (anthracofibrosis) patients and non-anthracotic control group were enrolled in meta-analysis. Tuberculosis should be confirmed and further investigation is not recommended. The incidence of tuberculosis among patients on steroids for treatment of autoimmune and other respiratory disorders poses a danger of reactivation of tuberculosis. Patients receiving immunosuppression (non-antiTNF) are generally offered a baseline CXR only. This potential susceptibility was investigated further.

Results: Twelve studies (8 studies on anthracofibrosis and 4 studies on anthracosis as a general term) comprised of 6280 patients were entered in this meta-analysis. Frequency of tuberculosis in all anthracosis subjects was 22.5% (32.6% for anthracofibrosis and 17.2% for anthracosis) which were significantly higher than control group. Determination of risk showed that cumulated odds ratio of tuberculosis in all studies of anthracosis was 3.16 (95% Cl= 2.49-6.85) which revealed significantly higher risk than control group. Subgroups analysis showed cumulated odds ratio of tuberculosis in subgroups of anthracofibrosis (3.28; 95% CI=2.16-9.12) were significantly higher than anthracosis as a general term (2.85; 95% CI=1.73-6.61).

Conclusion: Association of tuberculosis with all type of anthracosis of lung was confirmed and further investigation is not recommended.

P2588

Vitamin-D supplementation in patients with new smear positive pulmonary tuberculosis (PTB) with reference to sputum conversion

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Back ground: PTB is major problem in developing countries like india. Role of vi-D as immunomodulator which also suppresses growth of mycobacterial bacilli in macrophages, helps in treatment of PTB and early sputum conversion.

Methods: Study includes 60 patients of sputum positive PTB above age of 15 yrs with sex ratio 1:0.7. From may 2009 to October 2009 to avoid seasonal variation. All patients were divided in to 2 groups randomly: one group (28 patients) received ATT only and other group (32 patients) received ATT with oral cholecalciferol (vit d) 60.000 IU daily for 5 days. serum vit D were measured pretreatment and at every 2 weeks for 8 weeks. other measurements like sputum smear for AFB, Hb etc also measured.data were analysed.

Results: There is significant increase in Hb at 8 weeks (P=0.03), Decrease in mean ESR at 8th week (P=0.001) and increase in weight gain after 8 weeks (P=0.0312) in group who received vit D along with ATT.

There was early sputum conversion in patient who received vit D and ATT but this difference was not significant stastically so further study with large sample is required.

P2589

Steroids related tuberculosis: Does a subgroup require a more cautious approach?

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Background: Increased use of steroids for treatment of autoimmune and other respiratory disorders poses a danger of reactivation of tuberculosis. Patients receiving immuno-suppression (non-antiTNF) are generally offered a baseline CXR only. This potential susceptibility was investigated further.

Results: Our TB service treats 250 patients/year. Over 24 months, 4 patients requiring steroid therapy for primary lung pathology developed TB. 24 patients with no lung pathology were matched.

TB/Stereoids

Only 2 cases of TB have been detected in patients given steroids for a non-pulmonary cause.

Discussion: A previous meta-analysis had concluded TB occurred more frequently in patients receiving steroids but was not statistically significant.[J Intern Med 1994;236:619]. Specifically a prospective study in steroids for lung disease had commented on an incidence of 4.9%.[J Am Phys Ind 2000:48:881]. In our centre, reactivation was limited to patients with underlying chronic lung pathology, of ethnic origin not born in UK.

Conclusion: The incidence of TB among patients on steroids for lung pathology, born in areas of high incidence is unacceptable high and it seems prudent to investigate and treat them for latent tuberculosis before embarking on steroid therapy. This is particularly relevant for respiratory departments who deal with a high proportion of ethnic population. Further case controlled prospective evidence is required to define this relationship.

P2590

Determining psychological characteristics of newly diagnosed TB patients using Lüscher test

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The course of pulmonary TB depends, to a great degree, on the state of regulatory mechanisms (of CNS and psychic sphere) that determines patients’ adaptation and their ability to adequately withstand stress. We used Lüscher Color Selection Test to determine the objective psychological characteristics of our patients. 46 newly diagnosed patients (36 males and 10 females aged 21 to 71) were tested. 30 healthy individuals were tested as a control.

Results: The color green was the most frequently selected in the TB patient group. Mean (age) 50; 38.65; 45. Sex: Female (4); M (1); P (1). Disorders: Sarcoidosis (3), Lymphoma, Auto-immune Interstitial pneumonitis (1); Lung cancer. Steroids(mean dose, duration in weeks): 30mg, 5 weeks; 30mg, 4 weeks; 15mg. Organ: Lung (4); Lung (1), Spinal (1). Matched patients: Only 2 cases of TB have been detected in patients given steroids for a non-pulmonary cause.

Discussion: A previous meta-analysis had concluded TB occurred more frequently in patients receiving steroids but was not statistically significant.[J Intern Med 1994;236:619]. Specifically a prospective study in steroids for lung disease had commented on an incidence of 4.9%.[J Am Phys Ind 2000:48:881]. In our centre, reactivation was limited to patients with underlying chronic lung pathology, of ethnic origin not born in UK.

Conclusion: The incidence of TB among patients on steroids for lung pathology, born in areas of high incidence is unacceptable high and it seems prudent to investigate and treat them for latent tuberculosis before embarking on steroid therapy. This is particularly relevant for respiratory departments who deal with a high proportion of ethnic population. Further case controlled prospective evidence is required to define this relationship.
group, indicating defensiveness and passive aggressive reaction (14 first-choice selections). The color violet, corresponding to maladaptation, personality problems, individualism and emotional immaturity, followed closely (11 selections). The color yellow was third (6 selections). It reflected defensiveness, desire to communicate and expansiveness. Lastly, the color black (5 selections) reflected protest against the situation.

In the control group, almost all the colors of the main group were predominantly selected (red -8 selections, yellow -7, violet -5, green 5 and blue -3) indicating satisfactory adaptation abilities of this group. In the TB patient group, on the contrary, only two colors of the main group were selected with sufficient frequency (green -14 and yellow -11). This group showed preference for violet (second-frequent) and even black, which correspond to hesitancy, emotional imbalance, excessive sensitivity and the feeling of being stonewalled.

Conclusion: Lüscher Color Selection Test revealed signs of maladaptation, personality problems, instability and frustration in TB patients.

P2593
Adults without HIV infection hospitalised for tuberculosis – Clinical and drug sensitivity profiles
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Background: Tuberculosis (TB) remains a major health problem and an important cause of hospitalisation for severity.

Aims: To evaluate clinical and drug sensitivity profiles of patients without HIV infection hospitalised for TB.

Methods: A retrospective study of adults admitted for TB to a tertiary hospital between 2007-2010, without HIV infection. Age, gender, clinical presentation, co-morbidities, radiological findings, diagnosis, drug sensitivity, therapy and outcome were evaluated.

Results: The study included 207 patients, 18 to 89 years (mean 54.3 years). Of all, 69.6% had pulmonary TB, 10.1% pleural TB, 12.6% disseminated disease and 0.6% meningitis. There was sensitivity to all first line TB drugs in 85.2% cases, mono-resistance in 10.9%, poly-resistance in 3.3% and multi-drug resistance in 0.5% (a extensively resistant case). Streptomycin (12.6%) and isoniazid (6.0%) had the highest resistance. Death occurred in 22 patients (10.6%), 86.4% had severe co-morbidities. The other patients were transferred to other hospitals (7) or discharged to out-patient TB clinics (178), 99 of them also referred to hospital consultations.

Conclusions: In this group of patients co-morbidities were frequent, mortality was relevant and pulmonary TB was predominant as expected. TB drug sensitivity profile was not significantly different from ambulatory patients.

MONDAY, SEPTEMBER 26TH 2011

P2594
Post-menopausal mammary tuberculosis – Report of three cases
Khaid Bouit, Karima Marc, Rachida Zahrani, Jouada Benamar, Jamal Eddine Bourkadi, Mouna Soualhi, Ghali Iqra, Department of Respiratory Disease, Hospital Moulay Youssif, Rabat, Morocco

Breast tuberculosis is a rare disease, responsible of 0.6 to 4.5% of all breast diseases. It poses the problem of differential diagnosis with breast cancer. It is rare among men, children and after menopause.

The authors report on the following three new cases of postmenopausal breast tuberculosis:
- The first patient had right breast tuberculosis (2 nodules) with pleuro-pericarditis and miliary tuberculosis. She was placed under SRHZE association and steroid therapy.
- The second patient had right breast tuberculosis (1 nodule) with a homolateral axillary lymphadenopathy and no other tuberculosis localizations. A RHZ therapy was started.
- The third patient had association of right breast cancer treated by mastectomy followed by radiotherapy, and homolateral breast tuberculosis treated by RHZE. After few months, clinically significant changes in symptoms and mammography were observed in the first two cases while the third one had no symptoms. The therapy was maintained during 6 months. The three patients had remained stable for 24 months after the diagnosis. No recurrence was observed. Through these three cases, the authors will describe the epidemiological, clinical and contextual problems and pathogenesis of post-menopausal mammary tuberculosis.

P2595
The particularities of pulmonary tuberculosis (TB)-diabetes mellitus (DM) syndrome in a community with high prevalence for TB
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It is well known that patients with DM had a greater risk for TB. Our city is known with one of the highest prevalence of TB in our country. Aim to investigate the features of TB-DM syndrome.

We made a case control epidemiologic study - on 292 patients hospitalized between 2005-2009; we enrolled 146 patients diagnosed with new case-TB (group 1) and 146 controls without TB (group 2). We performed statistical analysis using SAS software version 9.2.
Tuberculosis (TB) is one of the leading causes of morbidity and mortality in renal transplant recipients. Due to the chronic immunosuppression the diagnosis is difficult. 

Aim: The aim of our prospective study is to determine the frequency and outcome of TB after renal transplantation.

Material and methods: For the period of 31 months were examined 52 patients after renal transplantation with pulmonary complaints. To diagnose the patients were used different non-invasive and invasive methods for diagnosis.

Results: In 5 cases (9.61%) were proved active tuberculosis. The mean age of these patients was 45 years (range 34–55 years) and mean time from transplantation to diagnosis was 94 months (8–180 months). The pulmonary infiltrative form was the most common form (60%), 1 patient was with pleural effusion (20%) and disseminated TB occurred in 1 patient (20%).

The diagnosis was proved bacteriologically on respiratory specimen cultures in 4 cases (80%) and histology in 1 case. The immunological tests for tuberculosis were positive in all 5 patients. In 3 patients (60%) there was co-infection with cytomegalovirus. The 3 patients (60%) were successfully treated with four-drug combination therapy. 1 of the patients lost blood urea nitrogen and creatinine after treatment.

Conclusion: TB is one of the most common infections among renal transplant recipients. Early diagnosis by using immunology tests and invasive methods, treatment of CMV-infection and effective therapy may improve graft survival and reduce the morbidity and mortality from this condition.

## P2599

### Tuberculosis is common in ethnic minority patients with chronic kidney disease in United Kingdom, and there is a high level of drug resistance

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Introduction: Chronic kidney disease (CKD) is more common in ethnic minority groups in UK and these patients have a high incidence of TB. We performed a study to characterise ethnicity and resistance patterns of patients with CKD and TB at a large renal unit in London.

Methods: 40 CKD patients who developed TB from 1994-2010 were analysed retrospectively. Patients were categorised by country of birth and time spent in the UK prior to development of TB, divided into <5 years or >5 years. Resistance patterns were sought as well as HIV status and Vitamin D levels.

Results: Ethnicities were: 15 Black-African, 9 Asian, 7 White-British, 6 Black Caribbean, 3 White-Other (including eastern Europe). 27 patients were non-UK born (67.5%) and 4 had lived in the UK for <5 years. Vitamin D levels were low in all patients. Of the patients, 10 (25%) had history of TB treatment.

Conclusion: Most CKD patients with TB were from ethnic minorities not born in UK. Most had lived in UK for >5 years suggesting TB development was not linked to duration in UK and that CKD is in itself a big enough risk factor. Vitamin D levels were low, as expected in both TB & CKD. Drug resistance (12.5%) was higher in ethnic minorities & HIV+ve patients with CKD, compared to background rate (4.9-6.1%). Hence it is important to look out for TB in ethnic minorities with CKD & also for drug resistance.

Number and proportion of tuberculosis cases with drug resistance by country, UK, 2008. www.hpa.org.uk

## P2600

### Smoking is a risk factor for TB infection, but is it an additional mortality risk?

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Aim: To investigate smoking habits of patients (pts) died of TB and successfully treated TB pts.

Material and methods: Comparative study of epidemiological data of TB deaths and TB pts, 135 in both groups, none HIV positive, in 2000-2009.

Results: 135 TB deaths occurred (mortality rate 6.4%, 76.6% of them died of TB.

TB deaths: male were 76.3% (103 pts), aged 18-88 years, (1.6% under 25y, 14.6% pts aged 25-44 yrs, 45.2% pts aged 45-64y, 38.6 over 65y). Smokers 81%, kofing 7.8 months before admittance, average weight loss was 10.2kg. 

TB pts: Of 135 pts male were 65.2% (88pts) aged 17-88 years, 8.3% under 25y, 25.8% aged 25-44y, 31.8% aged 45-64y, 31% over 65), 51% (69pts) smokers kofing before admission for average 4,1 months (1-12), average weight loss was 3.4kg (0-10).

Conclusion: In TB deaths group were more smokers (4/5 vs 1/2), older (84% over age 45 yrs vs 34% under age 44) and more male (76% vs 65%) than in the other group. They were kofing almost twice longer and had 3 times bigger weight loss before admittance. This delay may be due to fact they consider kofing as normal for smokers, but also as a result of confronting factors (alcohol use, socioeconomic).

Tobacco control should be incorporated in TB control.
P2601
What about asthma in tuberculosis patients
Hafza Zabi, Leila Felkhi, Iness Akrou, Eya Tangour, Hela Hassene, Dorra Greb, Sooraya Fenniche, Hajer Ben Abdelghaffar, Dalenda Belabbb, Monamed Lamine Megdiche. Service Ibn Nafis, Hôpital Abderrahmen Mami, Ariana, Tunisia

Introduction: The association of asthma and tuberculosis is rare but may raise particular issues around patient management. The aim of this study was to evaluate the control of asthma in tuberculosis patients.

Patients and methods: We describe a retrospective study, which included ten asthmatic patients with tuberculosis during the period between June 2001 and June 2010.

Results: Five men and five women were included, mean age was 37 years. Seven of them had pulmonary tuberculosis and three had lymphatic nod tuberculosis. Two patients had mild asthma, seven had moderate asthma and only one had severe and corticosteroid-dependent asthma. Seven patients had controlled asthma when tuberculosis diagnosis was established. Asthma treatment was based on inhaled corticosteroids and long-action Beta-2-agonists. During anti-tuberculosis treatment two patients developed near fatal asthma. Long-term stable asthma control was achieved over a time course of three to eight years.

Conclusion: The association of asthma and tuberculosis can lead to potential therapeutic difficulties because of pharmacologic interactions between anti-tuberculosis therapies and treatments for asthma treatment. In addition, asthma following treatment for tuberculosis appears to be well controlled.

P2602
A case of pulmonary tuberculosis combined with tuberculous goniaitis in a 12-year-old immigrant patient with haemophilia A
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Introduction: 9.4 million new tuberculosis (TB) infections and 14 million prevalent cases of TB were recorded worldwide in 2009 [1]. Hungary is a low incidence country with an incidence of 14.4 per one-hundred-thousand in 2009.

Case report: A 12-year-old Afghan boy was admitted to the hospital with pulmonary TB. Haemophilia A and a swelling of his left knee. He presented symptoms of coughing, haemoptysis and swelling of the left knee for one year. Pulmonary TB was diagnosed in Pakistan and was treated with rifampicin, pyrazinamide and ethambutol for 43 days and amputation of the left knee was suggested. He was transported to Hungary to find an alternative therapy to his knee. With physical examination cachexia, and diminished breath sounds over the apical right lung segments of superior lobe of right lung.

Conclusion: This case calls the attention to the immigrants’ TB screening.

Reference:

P2603
Pulmonary tuberculosis resides: A report of 44 cases
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Introduction: TB relapse is defined as any case of pulmonary tuberculosis treated, cured, and in whom TB is diagnosed on the basis of a smear or culture bacteriologically positive. it incidence in Algeria is 4.97%.

Aims and objectives: The aim of our study is to clarify the characteristics of the epidemiology, predisposing factors and diagnosis aspect of TB relapse.

Methods: We describe a retrospective study concerned 44 cases of pulmonary tuberculosis resides control, among 2257 patients, treated for pulmonary tuberculosis in the TB control unit of Blida between January 2005 and December 2009.

Results: Our series has assembled 27 men and 17 women with a mean age of 37 years. 86% of cases have already been treated for over one year for pulmonary tuberculosis. Comorbidities were found in 39% of cases, including diabetes (16% of cases) and psychiatric disease (6% of cases). The study notes the occurrence of relapse in 41% of cases during the first quarter of the year. Bacteriological confirmation of relapse by smear sputum was positive in 95% of the cases, the confirmation of relapse by culture was positive in 5% of cases. The bacteriological test was positive in 16% of cases. The empirical treatment was failed in 54% of patients. The cure rate was 95% of cases, the treatment failure was 4 cases and the treatment default was 4 cases.

Conclusion: We emphasize the frequency of relapse tuberculosis and their need for adequate care with regular monitoring to avoid the transition to chronicity.

P2604
Unusual forms of pulmonary tuberculosis
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Pulmonary tuberculosis PT is generally easily recognized by its classic features. Nevertheless, the radiological setting could be misleading, suggesting other diagnoses. We report 51 cases of PT with unusual in appearance and site (pseudotumoral 14 cases, endobronchial 25 cases, basal 6 cases and balloon release 4 cases). It occurred in 30 males and 21 females with a mean age of 40 years old (range age 15-71 years old). Twenty males were smokers. The clinical setting was dominated by bronchial syndrome, chest pain and haemoptysis. Chest X-ray showed pulmonary opacities-like tumor in 14 cases, retractable opacities in 20 cases, enlarged mediastinal lymph node in 5 cases, basal excavated opacities in 10 cases and a balloon release in 4 cases. Bronchoscopy showed endobronchial granulomas in 15 cases, bud-like tumor in 8 cases and mediastinal lymph node fistula in a bronchus in 2 cases. Chest scan highlighted a peripheral tumor-like process in 6 cases and a balloon release in 4 cases. The diagnosis of PT was confirmed by bacilloscopy in 6 cases, bronchial aspirate in 26 cases, bronchial biopsy in 20 cases, transmural biopsy in 6 cases, biopsy under thoracoscopy in 4 cases and an open surgical biopsy in 3 cases. Under antibacillary therapy, the evolution was favorable in all the cases. Despite their rarity, unusual forms of tuberculosis should be better known as it could simulate cancer especially in its particular pseudotumoral form.

P2605
Paradox radiologic progression despite appropriate antituberculosis therapy
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In this study we report a HIV negative case who got worse paradoxically in the course of antituberculosis therapy. A 68-year old male patient applied with complaints of cough, chest pain, and weight loss. Chest computed tomography revealed an irregular nonhomogeneous opacity involving the apical and posterior segments of superior lobe of right lung.

At the end of the first month of therapy radiological lesions increased. There was no endobronchial lesion on bronchoscopy, and no acid-fast bacilli in bronchial lavage fluid. Therapy protocol was not changed but radiological lesions regressed gradually. In conclusion, temporary deteriorations can occur in previous pulmonary infiltrates in patients who are under appropriate antituberculosis therapy. The gold standard for monitorization is microbiological methods but not radiological ones. Comorbid conditions, drug reaction and treatment failure is important in the differential diagnosis.
Baseline and treatment completion chest radiographs in pulmonary and extra-pulmonary tuberculosis

Background: Chest radiographs (CXR) are key to the diagnosis & management of tuberculosis (TB). End-treatment CXR (E-CXR) provide information on therapy response & risk of post-treatment pulmonary sequelae.

Objectives: 1. To report factors associated with baseline CXR (B-CXR) in pulmonary TB (TB) & extra-pulmonary TB (EPTB).

Methods: Of 305 patients, 113 (37.0%) were diagnosed with PTB, 155 (50.8%) with EPTB & 37 (12.1%) EPTB+PTB. 285 (93.4%) had B-CXR performed in the correct time period (early/late 5.6%, not performed 1.0%) with no significant difference by TB clinical status. Female patients were less likely to have a B-CXR (F: 89.6%, M: 97.4%, p < 0.001) which remained significant in multivariable analysis. 149 (52.3%) had E-CXR: more likely in those with abn B-CXR (63.1% abn B-CXR 23.8% normal, p < 0.001). 116 of 198 (58.6%) with abN B-CXR had an E-CXR with radiology review available. Of these 24 (20.7%) had abN E-CXR including HR, a Fluoroquinolones and at least 1 second line injectable therapy.

Results: Of those patients, 38% (8/21) failed to follow up without known reason, only 3 patients stopped Rx due to SE. Conclusion: Good compliance is achievable with patient education and close follow-up. Treatment side effects of LTBI are usually mild and self-resolving.

References:
Materials and methods: In 2009-2010, a total of 356 patients were treated, including 419 patients (33 new and 366 previously treated cases which had positive cultures with MDR strains. The testing of this MDR strain was performed by indirect method of proportion to second line drugs for critical proportion 0.05.

Results: 1. For new cases results showed the confirmation of MDR strains 8.3%; resistant to INH+RMP+Km 2.6%; resistant to INH+RMP+OFX 0.2%; and XDR strains 0.95%.

2. For previously treated cases results showed the confirmation of MDR strains 49.64%; resistant to INH+RMP+Km 22.2%; resistant to INH+RMP+OFX 7.1%; and XDR strains 8.35%.

Conclusions: 1. The high percentage of MDR strains of previously treated cases 49.64% is due to large number of patients provide from our Excellence Center of MDR TB.

2. The percentage of XDR strains from MDR strains is 9.31%.

P2612

Epidemiological and microbiological characteristics of reported cases with multidrug-resistant tuberculosis in the Republic of Bulgaria for the period 2000-2009

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A retrospective study of all patients with multidrug-resistant tuberculosis (MDR-TB) registered and reported in Bulgaria during the period 2007-2009 was performed.

Aims: To make epidemiological and microbiological characteristics of all cases with culture confirmed MDR-TB recorded and reported in the country during the above-mentioned period.

Materials and methods: Case-based data for all TB patients recorded and reported by the regional TB health facilities for the period 2007-2009, data sent by the microbiological laboratories for TB diagnosis, and TB registries of the NRL-TB at the NCIPD were examined.

Results: According to the case-based data, a total of 149 MDR-TB patients (age range 18-87) were recorded and reported during the period 2007-2009, representing 5.3% of all tested with DST. Out of all MDR-TB cases, 107 (72%) were male. Fifty-six patients (38%) were new, and 93 cases (62%) were previously treated. Out of all registered MDR-TB patients, 88.6% were confirmed by the NRL-TB.

Conclusion: The case-based registries provide exact clinical, microbiological and epidemiological information, avoiding case duplication during the reporting period. The frequency of MDR-TB among previously treated TB cases is higher, mainly among the relapses and the defaulters after treatment.

P2613

Multi-drug resistance tuberculosis (MDR-TB) in Federation of Bosnia and Herzegovina during ten years

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Multidrug-resistant tuberculosis (MDR-TB) defined as TB caused by strains of Mycobacterium tuberculosis that are resistant to at least isoniazid and rifampicin. The aim of this paper was to describe the resistance patterns of MDR-TB in FB&H.

Material and methods: Retrospective analysis of the reported cases with MDR-TB in FB&H during the years 2000-2009 notified through drug susceptibility testing (DST) in 5 laboratories according to the recommendation of the WHO and IUATLD in Europe.

Results: Total cases with DST results: 1035 (never treated 913; previously treated 121) in 2000; 1036 (936;100) in 2001; 1034 (914;20) in 2002; 1036 (936;100) in 2003; 1125 (1045;80) in 2004; 769 (692;77) in 2005; 808 (727;81) in 2006; 951 (847;104) in 2007; 518 (471;47) in 2008; 581 (529;52) in 2009.

MDR-TB among never-treated cases: 1 (0.11%) in 2000; 2 (0.19%) in 2001; 4 (0.42%) in 2002; 1 (0.10%) in 2003; 4 (0.38%) in 2004; 4 (0.57%) in 2005; 2 (0.24%) in 2006; 7 (0.82%) in 2007; 3 (0.63%) in 2008; 0 (0.0%) in 2009. MDR-TB among previously treated cases: 2 (1.65%) in 2000; 7 (5.42%) in 2001; 9 (9.00%) in 2002; 1 (1.09%) in 2003; 6 (7.79%) in 2004; 5 (6.49%) in 2005; 3 (3.70%) in 2006; 10 (9.61%) in 2007; 9 (19.14%) in 2008; 1 (1.92%) in 2009.

Conclusion: Data from FB&H show relatively low prevalences of MDR-TB during ten years. The prevalent of MDR-TB remains low at 0.57% - 0.82% among newly detected cases and 9.01% - 19.14% among previously detected cases. Recent data also indicate a further decrease in MDR-TB. This decrease may likely be the result of well implemented DOTS. Establishing reference laboratory facilities with adequate capacity to supervise DST and surveillance activities in the country is a critical step in MDR-TB control and care.

P2614

First national survey results of mycobacterium tuberculosis drug resistance in Kosovo, 2007-2008

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Objective: To evaluate the prevalence of DR to the first-line anti TB drug among new and previously treated cases of pulmonary tuberculosis.

Method: A national survey during 2007-2008 has been carried out, using “100% sampling” method, according to WHO and IUATLD standards. Smear-negative pulmonary TB patients aged ≥15 years were eligible. Drug susceptibility testing using simple proportion method was performed against four first-line drugs, i.e., isoniazid, rifampicin, ethambutol and streptomycin.

Results: During one year enrolling period, 207 initial isolates of M Tuberculosis were analyzed. Out of them 172 (83%) were from new cases and 35 (17%) from re-treatment cases. Any resistance among new cases was 20.9% and 45.7% among re-treatment cases.

Conclusion: Low rates of MDR-TB in Kosovo are due to a well performing national TB control program.

P2615

Drug resistant tuberculosis among Greek and immigrant patients in a pulmonary department in northern Greece

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Introduction: The proportion of TB cases among immigrants is gradually increasing in Western European countries, posing a threat to disease elimination in the coming decades.

Aim: To evaluate differences in prevalence of drug resistant tuberculosis among native and immigrant patients treated in a respiratory department of a regional general hospital in Northern Greece.

Subjects - methods: Clinical records data of patients with tuberculosis (new detected cases-43, relapses-21) treated in our department during 2007-2010 were retrospectively studied.

Results: 64 patients were recorded, 50 males and 14 females, 38 natives and 26 immigrants recently moved from former Soviet Union countries. 13 natives (34.2%) and 17 immigrants (65.2%) patients presented with extensive disease. 13 (34.2%) natives and 10 (38.4%) immigrants received therapy for a second time due to relapse, interrupted treatment or treatment failure. Resistance was confirmed in 11 natives (28.9%) and 12 immigrants (46.2%) (p: 0.253). monoresistance in 11, polyresistance in 8 and MDR TB in 4 patients.

Resistance patterns

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<th>Resistance</th>
<th>Greeks</th>
<th>Immigrants</th>
<th>Sum</th>
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<td>INH</td>
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<td>PZ</td>
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<td>RF + PZ</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RF + SM</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>RF + PZ + SM</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RF + PZ + SM + PAS</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Conclusions: TB cases among immigrants tend to increase, contributing significantly to overall higher incidence rates. Immigrants also tend to present with more severe disease and emerge more frequent relapses and higher prevalence of resistant and MDR-TB.

P2616

Drug resistance pattern of mycobacterium tuberculosis complex at the main reference tuberculosis centre in Greece, 2000-2010

Panagiotis Zouz1, Pinelopi Sotiropoulou2, Apostolos Papavasilieou2, Konstantina Broupi2, Stavroula Katziadia2, Simona Karabela2, Konstantinos Gourgoulianis3, Konstantinos Konstantinou1, 112th Department of Pneumonology, Sotira Chest Diseases Hospital, Athens, Greece; 2Ann Tusor Chest Diseases Department, Sotira Chest Diseases Hospital, Athens, Greece; 3Department of Pneumonology, School of Medicine, University of Thessaly.
Phthisiology&Pulmonology, Kiev, Ukraine

Aim: The aim was to determine the current DR profiles and their prevalence among patients with chronic forms that level is 30-70%. Knowledge of drug resistance (DR) is important for treatment and to forecasting the outcome.

Methods: We studied 325 specimens decontaminated with NaLC-NaOH then inoculated onto Bactec MGIT960, and L.J. medium. We did identification to all positive specimen then inoculated onto Bactec MGIT and 55.7% with L.J. the rates of contamination for each of the systems was 19.6%, while 145 isolates (8,3%) were resistant at least to isoniazid and rifampicin. During chemotherapy 36 patients IIC-group and 34 from comparison group there were 4 patients with primary MDR, and 23 with primary drug resistance (not the combination of H&R). In comparison group there were 6 patients with primary MDR and 16 with primary drug resistance (not the combination of H&R).

Results: Over the period of 2007-2009, an annual increase in proportion and range of drug resistance was increasing in all TB patients; cases of XDR TB were reported regularly.

Conclusion: The majority of cases (73.66%) has secondary MDR and simultaneaously DR to first-line drugs and to s. Most common is DR profile – with maintaining sensitivity to INH and RIF in presence of additional resistance to the different number s. The smallest spreads have HRE and HRZ-profile.

P2519
Secondary drug resistance during an intravenous intermittent chemotherapy in newly cases TB
Tatyana Petrenko, Vladimir Krasnov, Medical, Nosovitskii Research TB Institute, Noosvits, Obkhoskaya St, 81a, Russian Federation

The purpose: To study frequency secondary drug resistance M. tuberculosis (SDR) during an intravenous (IV) intermittent chemotherapy in newly cases TB.

Methods: 76 pulmonary TB patients without previous chemotherapy enrolled in study IV intermittent chemotherapy (3 times a week) appointed to 38 patients (IC-group): isoniazid (H) and rifampicin (R) – 10 mg/kg IV, streptomycin (S) – 16 mg/kg intramuscularly (IM), pyrazinamide (Z) – 25 mg/kg per os. 38 patients received daily same doses of H, R, Z per os and S (IM as a group of comparison). Both groups were identical. We determined SDR initially and every 2 month of patient treatment during 5-14 months.

Results: Initially there were 16 patients IC-group and 11 in a comparison group with fully sensitive TB. In IC-group there were 6 patients with primary MDR and 16 with primary drug resistance (not the combination of H&R). In comparison group there were 4 patients with primary MDR, and 23 with primary drug resistance. Among chemotherapy 36 patients IC-group and 34 from comparison group became sputum negative after 3.17±0.4 and 2.7±0.5 months accordingly (p=0,17, Mann-Whitney U-test). During the IV intermittent chemotherapy SDR appeared at 5 patients, secondary MDR – at 1 from 5. In comparison group SDR appeared at 2 patients, secondary MDR at 3 from 4 (R= 1.24, 95%CI 1.34-1.75). The mean time of formation SDR appeared in 3±0.3 and 2±0.6 months accordingly (p= 0,03, Mann-Whitney U-test).

Conclusion: The occurrence risk of secondary MDR is lowered. SDR term is slower in IC-group than in group of daily treatment, in about 3 months from the start of chemotherapy. This term coincides with sputum negative results at patients of both groups.

P2620
Drug resistance among new TB cases and relapses
Punga Victor, Lariya Rusakova, Yakinsona Marina, Kapkoy Lev, Elvira Putova. Epidemiology, CTRI RAMS, Moscow, Russian Federation

Purpose of the study: To study prevalence and range of drug resistance (DR) of TB mycobacteria (MBT) among 41,574 new TB cases and 5,890 relapses in 14 RF territories over the period of 2007-2009.

Materials and methods: Analysis of MBT DR was performed based on the official and applied statistical data quarterly received at the Center of Monitoring, CTRI RAMS.

Results: Over the period of 2007-2009, the proportion of new cases with DR MBT increased from 30.9% to 40.1%, and with MDR TB - from 10.8% to 13.2%. In the group of relapses the incidence of DR (48.4% and 55.4%) and MDR (26.7% and 33.9%) was much higher than MDR in new TB patients. One third of new TB cases had bad resistance to isoniazid and streptomycin and 15.0-20.0% of new TB cases were resistant to rifampicin and ethambutol. Among TB relapses DR TB, MDR TB and any other resistance to isoniazid, streptomycin, rifampicin and ethambutol was reported 2-3 times more often than among new TB cases. Over the period of 2007-2009, the rage of drug resistance was increasing in all TB patients; cases of XDR TB were reported regularly.

Conclusion: Over the period of 2007-2009, an annual increase in proportion and number of DR cases was reported. Therefore, it is necessary to perform monitoring of quality of the laboratory tests, data collection and follow up of TB patients' groups. Knowledge of DR MBT range of patients allows performance of the adequate chemotherapy, its adjustment, evaluation of the epidemiological situation on TB and timely managerial solutions. Increase in prevalence of DR MBT is the result of the previous failed courses of chemotherapy.

P2621
Drug resistance in pulmonary TB patients: Analysis of dynamics
Ludmila Pankratova1, Ekaterina Pereselentsova2, Ludmila Vlasova2.
1Phthisiology&Pulmonology, Saratov State Medical University, Saratov, Russian Federation; 2Microbiology Lab, TB City Hospital, Saratov, Russian Federation

MBT drug resistance (DR) frequently causes lack of treatment efficiency in TB patients. The use of standard WHO treatment protocols has not brought about a MBT DR/MDR decrease: on the contrary, the share of patients with primary MDR has increased 15-27 times over the 2005-2008 period. In 2008, in some regions of Russia patients with primary MDR MBT constituted 20-25% of the total number of TB patient. In 2010, we conducted an analysis of MBT DR in 312 pulmonary TB patients

Less common are HRE and HRZ (21.67% and 10.0% respectively). The pre- dominance of HRS and HRSZ profiles was found in the 2-d group – 71 (31.69%) pts and 41 (25.0%) respectively. Totally HRS profile was in 99 (49,19%) pts. The 3rd highest spread has HRE and HRZ (17,97% and 3,57% respectively).

Conclusion: Background/ AIM: Drug-resistant tuberculosis (TB) is a major issue for Public Health. This study was conducted to assess the prevalence of drug resistance to M. tuberculosis at the main reference tuberculosis centre in Athens, Greece (Anti-Tuberculosis Department, ‘Sotira’ Chest Diseases Hospital).

Methods: We retrospectively reviewed 343 isolates of drug resistant M. Tuberculosis from two culture systems. We did collection data about demographic characteristics and drug susceptibility. Antimicrobial drug susceptibility was tested using the method of proportion with Lowenstein-Jensen and BACTEC MGIT System.

Results: A total of 1747 patients (new culture-positive TB cases from 2000 to 2010) were analyzed. Individual drug resistance was as follows: 242 isolates (13.9%) were resistant to isoniazid, 167 (9.6%) to rifampicin, 130 (7.4%) to ethambutol, and 227 (13%) to streptomycin. The overall resistance to any drug was 19.6%, while 145 isolates (8.5%) were resistant to at least to isoniazid and rifampicin (multidrug resistant, MDR) and 39 isolates (2.2%) were resistant to at least to isoniazid, rifampicin, any fluoroquinolone and one of three injectable second-line drugs (extensively drug resistant, XDR). We should notice that none of the patients was HIV-positive.

Conclusion: A significant increasing trend in resistance rates to the four first-line anti-TB drugs, and any other drug, was observed during the 11-year period. MDR-TB and XDR-TB have emerged as a major public health threat in Greece, considering the immigration trend and the country’s key-point. The development of "direct observed therapies" (DOTs) in Greece, according to WHO guidelines, is of great importance.
Background: The strongest risk factor for drug resistance is previous history of tuberculosis treatment. Currently the national tuberculosis control program recommends drug susceptibility testing in failures of retreatment cases. This study is being conducted to see the drug resistance pattern in failures and defaulters of initial treatment before starting a retreatment regime.

Methods: This study was conducted in the OPD of Thoracic Medicine JPMC Karachi.

Sampling technique: Non-probability purposive sampling.

Results: Among 60 selected patients of category 1 sputum smear positive, 14 (23.3%) were defaulters, 38 (63.3%) relapsed and 8 (13.3%) patients were of treatment failure.

Culture sensitivity has shown 58 (96.7%) positive patients and only two (3.3%) were negative.

Multidrug resistance was found in 15 (25%) patients. MDR cases were 6 (42.9%) among 14 defaulters, 4 (10.5%) among 36 relapsed and 5 (62.5%) among 8 failure treatment patients.

Rifampicin resistance was found in 20 (34.5%) patients. Isoniazid was resistant in 19 (32.8%) patients. Ethambutol was resistant in 21 (36.2%) patients. Pyrazinamide was resistant in 17 (29.3%) patients. Streptomycin was resistant in 10 (17.2%) patients. None of antituberculous drug was resistant among two culture negative patients. Multidrug resistance (MDR) was observed in 15 (25.9%) patients.

Conclusion: We conclude that levels of MDR-TB is very high in patients not responding to CAT1 anti tuberculous drugs in our community.

P2623 Impact of drug resistance over sputum conversion in tuberculosis patients receiving re-treatment regimen

Prem Parkash Gupta, P.T. Yasir. TB & Respiratory Medicine, PGIMS, Pt B D Sharma University of Health Sciences, Rohtak, Haryana, India

Background: Previous tuberculosis treatment is known to be associated with high drug resistance.

Objectives: To assess the impact of drug resistance over sputum conversion in tubercular patients receiving supervised re-treatment regimen.

Methods: A total of 101 smear positive pulmonary tuberculosis patients [relapse (65), failure (23), and defaulter (13); all with age ≥ 15 years] registered for re-treatment at our Institute were included. Drug susceptibility testing (DST) was done using Lowenstein-Jensen media. All patients were given thrice weekly supervised re-treatment regimen. Sputum microscopy was done in all patients at initiation and also at the end of 1st, 2nd, and 3rd months.

Results: 41.50% of patients in relapse group, 85.71% in failure group, and 70% in default group had drug resistance. Sputum conversion during initial three months in relapse group was 29.23%, 60%, 64.61%, respectively; same for failure group was 0%, 0%, 4.36%, respectively; and that for default group was 23%, 38.46%,

Table 1. Sputum conversion across first 3 months

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistant/sensitive</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>S (n=58)</td>
<td>42.10%</td>
<td>86.84%</td>
<td>94.73%</td>
</tr>
<tr>
<td></td>
<td>R (n=46)</td>
<td>2.17%</td>
<td>2.17%</td>
<td>2.17%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>S (n=53)</td>
<td>32%</td>
<td>64.15%</td>
<td>69.61%</td>
</tr>
<tr>
<td>R (n=51)</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>S (n=68)</td>
<td>25%</td>
<td>50%</td>
<td>52.94%</td>
</tr>
<tr>
<td>R (n=16)</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>S (n=59)</td>
<td>28.81%</td>
<td>57.62%</td>
<td>62.71%</td>
</tr>
<tr>
<td>R (n=25)</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
<td>nul</td>
</tr>
</tbody>
</table>

S = sensitive to drug; R = Resistant to drug.

Previous drug intake and subcategory were significant factors for drug resistance. It was also associated with smoking, poor education and economic factors but not with age or sex.

Conclusions: We observed significant drug resistance; highest for failure subcategory followed by default and relapse ones. Such high drug resistance requires DST at start of tubercular re-treatment in all patients.

P2625 Clinical characteristics and mortality patterns of MDR-TB patients in India

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Introduction: This study gathered information on genesis of MDR TB at 3 centers in India which helps understand the current clinical practice and management of MDR TB and helps to standardize diagnostic and therapeutic strategies relevant for resource poor setting.

Primary objective: To describe the clinical profile, of patients with MDR TB and suspect MDR TB patients in India and their out come.

Study design: Descriptive follow up study.

Study setting and population: Private and public health sector: Patients attending primary, secondary and tertiary health care centers in selected study areas in India.

Study period: 1st June 2007 to 30th May 2009.

Study Variables Clinical Outcome Measures: Cure - Patients treated for 18 - 24 months and who remain smear and culture negative; Likely cures - patients treated for at least 12 months, and who remain smear and culture negative; Absconders/Defaulters and Death.

Results: 344 cases, either suspect or confirmed cases of MDR-TB from 3 different states in India were recruited. 71 cases were culture rve for MDR TB. 15.77% patients died. 59.54% of the patients had far or moderately advanced chest X-ray lesions. The BMI of patients who died was less than 20 (87%). 27.4% of the patients who died had diabetes. 7.5% were males. Smoking index was moderate to heavy for 25%. More than 50% of the patients were aged between 30 - 50. 58% of patients had previous treatment with 4 drugs and 10% had received second line drugs. 67% of the patients utilized government facility for their treatment. With proper treatment success was > 60%.

Conclusion: MDR-TB if not treated can lead to early death among patients with low BMI. Diabetes Mellitus and far advanced chest X ray lesions.
P262
Resistance pattern to WHO CAT IV regimen in patients suspected of drug resistance tuberculosis presenting to a specialist office practice in Mumbai
Parag Chaudhari1, 2, Arvind Kate1, 2, Joerg Leuppi1, Michael Tamm1, Prashant Chhajed1, 2, 3

Sr. No 2nd line anti-TB drugs Resistant (n) Resistance (%)
1 Isoniazid 21 77.78
2 Ethambutol 12 44.44
3 PAS 15 55.56
4 PZA 18 66.67
5 Streptomycin 20 74.07

Conclusion: The occurrence of in vitro drug resistance to category 4 anti TB drugs is very high, which is expected to have direct effect on tuberculosis. This poses challenges to administration of empiric anti TB treatment.

P267
Multidrug-resistant tuberculosis in a kidney recipient
Ventsislava Pencheva, Daniela Petrova, Ognian Georgiev.

Multidrug-resistant TB (MDR-TB) was proved in this patient. Antituberculosis treatment with four medications from second line was started.

Tuberculosis is a frequent infectious complication in patients on renal replacement therapy, as a result of immunosuppression from uremia and drugs in the post-transplantation period. The frequency of MDR-TB increases in last years. That requires treatment with second line drugs for longer period than patients infected with drug-sensitive strains and is with higher mortality rates.

P268
Dynamics of production thyroid-stimulating hormone in patients with multiple-drug resistant tuberculosis (MDR-TB) on the background of prolonged chemotherapy
Tatiana Morozova, Tatiana Salina. Department Phthisiologu, Medical University, Saratov, Russian Federation

Treatment of patients with pulmonary tuberculosis with MDR-TB requires the use of drugs 2 rows that have a large number of adverse reactions. It is assumed that prolonged simultaneous reception of protonamide and PASK can reduce thyroid function.

Aim: Evaluation of trends in production of thyroid-stimulating hormone (TSH) in patients with MDR-TB on the background of prolonged combined chemotherapy.

Methods: TSH levels in serum were determined in 102 patients with MDR-TB, initially and after receiving patients 60, 120, 180 doses of a combination of antibiotic drugs (capreomycin, protonamide, pyrazinamide, PASK, ofloxacin, cycloserine) by immunonemoence method.

Results: The level of TSH in patients with MDR-TB before therapy was low (mean 1.57±0.19 mIU/ml). After receiving 60 and 120 doses of the drugs level of the TSH of patients increased (2.95±0.57, p=0.046 and 3.32±0.41 mIU/ml, p=0.006, respectively). Significant increase in TSH was observed in 20% of patients without clinical manifestations of hypothyroidism. On the background of receiving of drugs (180 doses) TSH levels decreased slightly (2.86±0.37 mIU/ml). Increased TSH persisted in 13% of patients.

Conclusions: In patients with MDR-TB in the background of the combined use 6 drugs observed increase in TSH levels in the absence of clinical signs of hypothyroidism. The downward trend in TSH levels with continued therapy with the abolition of drugs (180 doses) may indicate the inclusion of compensatory mechanisms, and at this stage of treatment does not require additional correction of thyroid function.

279. Tuberculosis epidemiology and public health

P269
Evolution of tuberculosis in an area of Vizcaya
Sandra Pedroza Tedaja1, Beogota Vilar Achabal2, Maria Alfonso Imizcoz1, Israel Lopez Mirones2, Luis Miguel Soria Riendas1, Nuria Marfa Malanda1, Ines Martinez Rienda2, Esteban Cienfuegos Ayuso1, Rafael Zalacain Jorge1, Elena Urra Zalbidegoitia2, 3.

Aim: To study the evolution of Mycobacterium tuberculosis (MT) over a period of 21 years in our area and to know the resistance rates to first-line antimicrobial drugs.

Material and methods: We studied all cases of MT infection diagnosed between 1989 and 2009 in our hospital, attending a population of 420.000.

Results: In this period, 2.164 cases of MT infection have been diagnosed. The mean incidence rate was 24.5 per 100,000 inhabitants per year (maximum 42.6 in 1992 and minimum 11.9 in 2008). The mean age was 48, with a higher incidence in the group of 30-49 years. The gender distribution was 1.8 men/women. In 262 cases there was coinfection with HIV (12.1%), with a maximum of 23.6% (n = 35) in 1993 and minimum of 2.5% (n = 2) in 2004.

The location was pulmonary in 74.2%, extrapulmonary in 20.1% and disseminated in 5.7%. In patients co-infected with HIV, the presentation was pulmonary in 61.4%, extrapulmonary in 13.4% and disseminated in 25.2%. 63 strains have been detected with some resistance (2.8% of general population, which corresponds to 3% in non-HIV and 1.5% of coinfected). There were 36 strains resistant to isoniazid (1.7%), 11 to rifampicin (0.5%), 3 to ethambutol (0.14%) and 25 to streptomycin (1.2%). 17 strains were resistant to more than one drug. Of these, 6 were resistant to at least isoniazid and rifampicin (MDR-TB).

Conclusions: 1. The incidence of MT has clearly diminished over the study period. 2. There has been no change over the years in terms of gender distribution, age groups and location of MT. 3. HIV co-infection has less importance as a risk factor associated. 4. Resistance to first-line drugs is rare in our area and maintains stable levels. 5. We have found some MDR-TB in the study period.

P270
Evolution of the incidence of tuberculosis in the ill health area of the Principado of Asturias, Spain
Jose-Maria Garcia-Garcia1, 2, Fernando Alvarez-Narvaez1, Manuel Villanueva1, Henar Villar1, Juan-Jose Palacios3, Jesus Allende1, Andres Sanchez-Antuano1, Manuel Martinez-Muizia1, Jose-Antonio Gullion1, Aida Fernandez-Pantiga1, Jose-Manuel Fernandez-Carrera1, Ana Fernandez-Quirga1, Begona Gonzalez-Gonzalez3. 1UGC Neumologia, Hospital San Agustin, Aviles, Asturias, Spain; 2Microbiologia, Hospital San Agustin, Aviles, Asturias, Spain; 3Unidad de Referencia de Micobacterias, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain; 4Investigation, Hospital San Agustin, Aviles, Asturias, Spain; 5Atencion Primaria, Area Sanitaria III, Aviles, Asturias, Spain.

Aim: Description of the evolution of the incidence of tuberculosis (TB) in the last 10 years and the different circumstances that can have influence on it.

Methods: We collected all the cases of cultured proven TB. We describe factors that can have influence: 1. Number of immigrants, HIV co-infection, immunosuppression (biological therapy included). 2. Molecular epidemiology. 3. Treatment follow-up. 4. Contacts study.

482s
Farmaceutici SpA. Visit Chiesi Farmaceutici SpA. at Stand D.30
MONDAY, SEPTEMBER 26TH 2011
Results: Our Health Area has 155,000 inhabitants and we had 388 TB patients in 10 years, with a global incidence of 25/100,000 population per year (15/100,000 last year). 1. The percentage of immigrants, HIV co-infection and immunosuppression is small (figure 1).

2. The molecular study performed in 50 patients (2008-2010) shows clustering in 74%. 3. There were 389 patients treated with successful results (cure or treatment completion). 4. We had performed contacts study during all the period but we only know data since 2008 when we started a Pilot Programme (we studied 398 contacts of 152 patients, with 125 infected patients with preventive therapy).

Conclusions: We had a continuous decrease in the incidence of TB, mainly in the last year, with a small percentage of immigrants, HIV co-infection and immunosuppressive therapy, good therapy compliment, and a Programme of study of contacts in a region with recent TB transmission. All together can explain the decrease of TB incidence.

P2631
Epidemiology of tuberculosis in the province of Siena
Simonia Gianni, Paola Michele Oria.
Our Patients: Department of Pulmonary Diseases, Le Scotte Hospital, Azienda Ospedaliero-Universitaria Senese, Siena, Italy

The AA studied the epidemiology of tuberculosis (TB) from 2003 to 2008 in the Province of Siena. The population increased from 265,907 residents in 2003, to 288,378 in 2008. Its distribution in the districts was at 2008: Val d’Elsa (24%), Siena downtown (23%), Val di Chiana (23%), Val d’ Orcia-Amiata (9%), Creti-Val d’Arbia (9%), Chianti (6%), Val di Merse (6%). The immigrants at 2008 in the districts were: Chianti 10.9%, Val di Merse 10.5%, Creti-Val d’Arbia 8.4%, Val d’Elsa 7.9%, Val di Chiana 7.9%, Val d’ Orcia-Amiata 6.2%, Siena downtown 5.7%. In the period considered, TB constantly increased, and the % of 10 cases/100000 inhabitants of the countries with low incidence of TB, was exceeded in 2007 with 12 cases/100000 inhabitants, 10 cases/100000 in 2008. The incidence between the immigrants exceeded 7 times that between the Italians, from 30/100000 to 215/100000 residents for immigrants, from 4.2/100000 to 9/100000 of 10 cases/100000 inhabitants of the countries with low incidence of TB, was 2008 in the districts was: Chianti 10.9%, Val di Merse 10.5%, Creti-Val d’Arbia 8.4%, Val d’Elsa 7.9%, Val di Chiana 7.9%, Val d’ Orcia-Amiata 6.2%, Siena downtown 5.7%. In the period considered, TB constantly increased, and the % of 10 cases/100000 inhabitants of the countries with low incidence of TB, was exceeded in 2007 with 12 cases/100000 inhabitants, 10 cases/100000 in 2008. The incidence between the immigrants exceeded 7 times that between the Italians, from 30/100000 to 215/100000 residents for immigrants, from 4.2/100000 to 9/100000 residents for Italians; probably the incidence in immigrants was underestimated as the study considered only the notified cases and the regular immigrants. The greatest incidence of TB was in the districts of Val d’Elsa and Siena downtown. The immigrant TB patients were younger than Italian patients (35±15 vs 56±20 years old, p<0.05). The 86.4% of the 142 patients examined were affected by TB diagnosed for the first time, the 13.6% by relapses of TB. No significant differences were found concerning the incidence of pulmonary and extra-pulmonary TB, the 66.4% of Italians were affected by pulmonary TB, the 28.2% by extra-pulmonary TB, the 5.4% by pulmonary-extra pulmonary TB; the 68.6% of immigrants were affected by pulmonary TB, the 26.8 by extra-pulmonary TB, the 4.6% by pulmonary-extra pulmonary TB).

P2632
A 3 year (2007-2010) tuberculosis treatment analysis in Belfast City Hospital, Northern Ireland
Ihzaq Masih, Anne Bren, Shepherd Richard, Cecelia O’Kane.
Respiratory Medicine, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom

Introduction: Tuberculosis is on the rise globally. Northern Ireland is facing the enormous task to identify, diagnose and treat tuberculosis. Anti-tuberculosis treatment can be tedious and the side effects can hamper management and outcome.

Objectives: To note the prevalence among local and immigrant patients, ascertain the HIV status and concordance and tolerance of anti-tuberculosis drugs.

Methods: A retrospective clinical notes review, microbiology and biochemistry laboratory record analysis.

Results: In total 92 patients, half were originally from Northern Ireland [Table]; 61% male and 39% female. The mean age was 50 (± 21) years with a bimodal age distribution between immigrants (36±11 years) and local patients (66.5±15.5 years).

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Ireland</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>Indian Subcontinent</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Africa</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Far East</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
| Total             | 92    | 100%

The majority (67%) had pulmonary and 20.5% had lymph node involvement. Rest had skin, bone, peritoneum, and periasc abscess disease. Culture positive were 76% and smear positive 45%. The majority (79%) were fully and 4% were partially sensitive to the treatment. One patient was multi-drug resistant. Four percent had HIV. The commonest side effect was minor GI upset (7%). Hepatitis and arthralgia occurred in 5.5%, minor skin reactions in 3%, and renal impairment, peripheral neuropathy, febrile reaction and retrobulbar neuritis in 2% each. Seven percent of patients received directly observed therapy.

Conclusion: Tuberculosis is increasingly prevalent among the local population. Only 4% were HIV positive. Good drug compliance was observed in two third of patients. Treatment was modified in 24%, no treatment was stopped.

P2633
What patients account for the post-socialist increase in pulmonary tuberculosis?
Alan Altraja1, Peter Viiklepp2, Kai Klimum1, Heinart Sillaste1, Lea Pehme3.
1Department of Pulmonary Medicine, University of Tartu, Tartu, Estonia;
2Estonian Tuberculosis Registry, National Institute for Health Development, Tallinn, Estonia;
3Lung Clinic, Tartu University Hospital, Tartu, Estonia

Background: After a steady decline in tuberculosis (TB) from 1954 (417/10^5 yr) to 1992 (211/10^5 yr), along with the overwhelming societal and health care changes after independence was declared in 1991, Estonia experienced a resurgence of TB incidence since 1993, which peaked at 47.5/10^5 yr in 1998, without immigration playing a major role.

Aims: To reveal whether patients with particular characteristics accounted for the increasing incidence of pulmonary TB (PTB) in the changed societal conditions (1995-2003) compared to the “low incidence period with a decrease” (1985–1991) to determine the populations under significant risk in such circumstances.

Methods: TB-related characteristics of all PTB cases diagnosed during 1985–1991 (n=362, median age 43.6 yr) and 1995–2003 (n=668, median age 44 yr) in Tartu city and county in Estonia were subjected to logistic regression analysis to find determinants of PTB characteristic of the independence period.

Results: During independence, there were significantly more smear-positive patients (OR 2.39, 95%CI 1.57-3.64), those who sought help because of symptoms (OR 2.40, 95%CI 1.73-3.31), and those who had had TB contact (OR 3.83, 95%CI 2.45-4.68), but significantly less alcohol abusers (OR 0.60, 95%CI 0.42-0.87), and those with a cavity (OR 0.66, 95%CI 0.46-0.96) and a limited disease (OR 0.55, 95%CI 0.31-0.95).

Conclusions: Despite continuously free access to care for TB, the common social groups like non-alcoholics and non-smokers more often fall ill with culture-confirmed non-limited PTB and account for the increased incidence of TB after the post-socialist changes.

Funded by an ESF grant No. 8118.

P2634
Epidemiological investigation in TB diagnosis must be reconsidered
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Aim: The purpose of this study is to prove the importance of the epidemiological investigation in early TB diagnosis.

Material and method: We have analyzed the TB cases registered in three adult tuberculosis districts in Iasi, Romania. The patients have received TB treatment during 2010. We used the medical records, district records and IT records.

During this period, we treated 211 TB patients: 178 pulmonary TB and 33 extra-pulmonary TB cases; we have recorded 168 new cases, 32 relapses, 10 patients were readmitted after failure, default, MDR chronics and one transfer. Using epidemiological investigation, we identified 22 cases (10.43% out of all analyzed cases). The medical history of the patients revealed that 84 of them (39.81%) had previous TB contact: 86.9% of these had domestic contact and only 13.1% of them had indirect TB contact.

Conclusion: Out of the 211 cases, only 22 have been identified using epidemiological investigation. The medical history of 84 patients revealed TB contact, especially domestic TB contact. Moreover, in a single family, 4 domestic contacts developed pulmonary TB during the past 20 years. They all manifested the same type of drug resistance. This fact has been determined by using epidemiological investigation.
We must reconsider:
- the periodic screening of TB contacts over a greater period of time;
- the key role of the family physician, who must be focused on evaluating a large number of indirect/indirect TB contacts for a correct and efficient epidemiological investigation.

P2635
The development of tuberculosis in Bucharest in the last ten years
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Bucharest, capital of Romania, with a population of 1.944.500 inhabitants, constitutes an important problem of epidemiological surveillance of tuberculosis due to a high percent of floating population, numerous overcrowds of persons in locations that are deteriorating (8528 inhabitants/km²), existence of vulnerable groups (homeless, roma population, poor, immigrants) with a lower social, economic and educational level, increasing number of the unemployed, etc.

Objective: The study of the main indicators of the TB endemic in Bucharest in the last nine years.

Material and method: We used the information existing in the official documents of the information system within the National Program of Tuberculosis Control.

Results: A tendency of incidence increase has been installed, reaching from 65,9‰ in 1985 to 154,1‰ in 2001, after which a decrease occurred yearly, reaching 68,3‰ in 2010. A decrease of the incidence with 52% was recorded during 2001 – 2010. The incidence for new cases decrease from 135,8‰ in 2002 to 57,5‰ in 2010 and the incidence for relapses decrease from 18,3‰ in 2001 to 10,9‰ in 2010. The tuberculosis incidence in the 0-14 year children population decrease from 60,8‰ in 2001 to 22,6‰ in 2010. The source density was reduced from 12 sources/Km² in 2001 to 5 sources/Km² in 2009. The rate of the therapeutic success of the new source cases with pulmonary TB (M+) increased from 82,2% in the patient cohort from 2001 to 85,23% in those from 2009.

Conclusions: Tuberculosis control in Bucharest benefits from a rather complex material basis which should be improved according to the present day epidemiological conditions.

P2636
Increasing adherence to TB treatment – Pilot intervention in two counties in Romania
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Introduction: TB is a major public health concern in Romania. All health services are provided free of charge to TB patients and their contacts, through the National TB Programme. However default rate in new pulmonary smear positive cases is over 5%.

Aims and objectives: To measure the impact of a pilot intervention – giving small incentives – on the adherence to treatment of TB patients.

Methods: A pilot intervention, by giving to compliant patients small incentives (around 12 EUR per patient and per month, consisting in tickets for common goods) was unfolded in two counties of Romania (Iasi and Prahova), in the first half of 2009.

Results: During the study period 583 TB cases were registered in Iasi and 411 in Prahova and around 70% of them have received incentives. Percentage of TB patients taking all treatment doses until the final outcome was 93.1% in the first semester of 2009 versus 88.8% in the same period of 2008 in Prahova county. In Iasi county the percentages were 94.6% and 92.1% respectively.

Conclusions: The project induced a significant increase in proportion of patients that finalize the treatment in Prahova county (p=0.010), but not in Iasi county (p>0.090). Giving small incentives seems to increase the adherence to the TB treatment during for months.

P2637
The results of DOTS Plus project in Romania (2004-2010)
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Introduction: Although TB notification rate declined significantly in the last 8 years in Romania, from 142.2‰ in 2002 to 90.5‰ in 2010, MDR-TB cases still posed a special attention (812 such cases have been reported in 2009). The DOTS Plus project funded by Global Fund and started in Romania in December 2004 has as purpose to provide high quality health services to a part of MDR-TB patients in Romania.

Aim and objectives: To analyze and characterize treatment outcomes of MDR-TB cases enrolled in DOTS Plus project.

Methods: In the retrospective study have been enrolled 794 MDR-TB cases registered in DOTS Plus project between December 2004 and December 2010. Data have been collected from database of the project and National TB Register.

Results: From the total of 794 cases registered in the project and hospitalized in the 2 MDR-TB excellence centers in the country (57.5% in Bucharest and 42.5% in Iasi county), 67.7% were males and 32.3% females. Primary MDR was found in 26.6% of the cases. The DST pointed 49.3% with only HR resistance and 50.7% with other drug resistances (HR+1 to HR+5). 13 cases had XDR-TB. The ambulatory phase of the treatment was done at 119 TB dispensaries (62‰ from all TB dispensaries countrywide). The default rate decreased obviously from 31.5‰ in 2005 to 12.9% in 2008, consecutive to the distribution of different kind of incentives which improved treatment adherence. Success rate of the GLC patients (62%) was significantly higher than at the patients treated with NTP resources (24.2%).

Conclusions: The favorable evolution of MDR-TB patients enrolled in DOTS Plus project demonstrates real benefits and recommend its case MDR management extension to all MDR-TB cases in the country.

P2638
Assessing the risk of tuberculosis infection in a vulnerable population group (ethnicity rom) in a TB endemic population
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Introduction: High incidence of tuberculosis in our country is related primarily to a reduced standard of living for a part of the population nationwide, including a large segment of the population by ethnic group roman.

Aim: This study analyzes the prevalence of TB infection in vulnerable population groups, in an area with a high prevalence of tuberculosis (138‰/000), where BCG vaccination is mandatory.

Methods: A prospective study of detection of TB infection in the romen community from the west of the country (Arad and Timis), from July 2009-December 2010.

Results: Of 1417 persons who underwent tuberculin skin test (TST) to detect latent tuberculosis infection (LTBI), 700 persons (49,40%) had positive TST results. 73.42‰ the study participants had no BCG scar present in where BCG vaccination is mandatory in our country. 51.43% of those with positive TST were men. 71.20‰ had recently tb contact.

Conclusion: Considering the fact that TB in our country is a major public health problem in a vulnerable population group (ethnicity rom) should be applied consistently screening to identify latent tuberculosis infection.

P2639
Risk factors for anti-tuberculosis treatment failure
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The effectiveness of DOTS at new TB cases must achieve 95% in Moldova is 70%. The patients with increased risk for failure and relapse are marginalized people. The diagnosis, organization and supervision of the treatment is difficult and the rate of failure is very high. Intrinsic risk factors for treatment failure, those related to the patient, can be under control of the physician, instead extraneous factors, are not related to the disease, but influence the outcome: poverty, ignorance, contact with active TB, they must be covered by the national TB control programs.

We estimated risk factors for treatment failure at 96 new TB cases hospitalized in the municipal hospital of Chisinau. Intrinsic factors revealed were: male sex 69 cases (70%), young age 25-44 yrs, 65 cases (66%), severe forms: infiltrative TB 75 cases (76%) and fibrocavernous TB 9 (10%), disseminated infection 60 cases (61%) with bilateral extension 71 cases (72%), pulmonary bleeding 19 cases (20%), pleurisy 12 (13%), 23 of cases had a coexisting pathology (alcoholics 19 cases, smokers 17, COPD 20 cases, 6 HIV-infected), 3 pregnant women, 8 cases with adverse drug reactions with changing of the therapeutic schedules. The extraneous factors were poverty and bad living conditions 90 (91%) unemployment 66 (67%), low educational status 69 (70%), 46 (47%) had a familiar contact with a TB patient, 34 (35%) had MDR strains in the sputum culture. For 77 cases (78%) the diagnosis was established with a delay more than 3 months after the onset of TB. All listed factors associated with the errors in treatment have induced emergence of MDR-TB that contribute to more problems in management of TB control programs.
Monday, September 26th 2011

P2641
Tuberculosis and gender: Epidemiological trends since 1957 in Poland
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Aim of the study: To describe changes in TB epidemiology since 1957 in Poland in relation to gender.

Methods: Retrospective analysis of data from National TB Register.

Results: The incidence rates (IRs) of tuberculosis in general Polish population decreased much between 1957 and 2009 from 290.6 to 21.6 per 100,000. The constant regularity in this study period was that IRs among men were higher than among women in every adult age group. It happened that the IR in men group was more than four times higher in comparison to female group. In males the linear relation of IRs and age was observed with the peak usually in 50-59 age group. In women group the more complex pattern occurred. Till the end of nineteenth the bi-modal relation of IR with age was observed. Originally the highest IRs were among younger and oldest women. Since the end of nineties the distribution of IRs has been similar in both gender groups, namely the older age group the higher was IR of tuberculosis.

Conclusions: The big differences in IRs of tuberculosis among men and women were constantly observed in Poland between 1957 and 2009. The relation of IRs and age in both gender groups came to be similar in the end of nineties. The task is to explain the higher proportion of men among TB cases.

P2642
Tuberculosis treatment completion in migrants, St.-Petersburg, Russian Federation
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Introduction: Last years migrants in the Russian Federation (RF) are presented mainly by foreign citizens arriving to the RF from former Soviet republics visa-free with the aim of temporary labour activity. Some of these countries have high burden of tuberculosis (TB). These persons can move freely within the RF; they are not obliged to register at the place of actual residence and most of them have no health insurance. By law, TB is in the basis for the refusal or cancellation of temporary residence permits or work permits to foreigners in RF.

Objective: To assess TB-treatment completion rates in patients who arrived from countries visa-free with the aim of temporary labour activity.

Methods: In the absence of registration at the place of actual residence, health care staff can not locate the patient and ensure completion of treatment. If treatment can not be completed in the country of temporary stay, a patient transfer to their home country is required.

Results: Out of 128 selected patients (M:112 F:16) 22 patients (31%) refused treatment and died. Thus, only 27 patients (39%) completed treatment, the fate of 43 patients (56%) is unknown. Of the 48 patients who started treatment, 21 (44%) did not complete treatment due to various reasons. The total number of patients with drug sensitivity test (DST) were investigated. DST's were studied in 104 cases. The mid-year number of soldiers is 537200 in Turkish Armed Forces, the culture positive. Lung involvement was observed in 67.5% (175 patients), organ involvement was observed in 6 (5.7%) patients.

Conclusions: Although the incidence of tuberculosis in young soldiers is moderately high it showed a significant decline compared to a studied published 8 years ago. The results of primary drug resistance to tuberculosis drugs and multi-drug resistance rates were increasing. National Tuberculous Control Program had to be directed effectively to decrease antimycobacterial drug primary resistance and multi-drug resistance rates.

P2643
Incidence of tuberculosis and primary drug resistance rates in young Turkish soldiers
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Introduction: Tuberculosis is an important public health problem. Epidemiological results have to be used to control the disease. The aim of the study is to investigate incidence of tuberculosis and primary drug resistance rates in young conscripts.

Methods: Soldiers with tuberculosis between January 1, 2009 and December 31, 2009 is recorded retrospectively. Results of sputum culture positive cases and also cases with drug sensitivity test (DST) were investigated.

Results: All patients were male with a mean age of 22.51±4.63. The total number of newly diagnosed patients in 2009 was 259 while 121 of them were sputum culture positive. Lung involvement was observed in 6 (5.7%) patients.

Conclusions: Of the newly diagnosed patients in 2009 was 259 while 121 of them were sputum culture positive. Lung involvement was observed in 6 (5.7%) patients.

P2644
Drug resistance pattern of directly observed treatment shortcourse (DOTS) category-II relapse patients
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Background: Multi-Drug resistance (MDR) is an emerging threat to tuberculosis control and resistance pattern depends on factors like regimen, duration of treat- ment, compliance etc. Currently Cat-II relapses are retreated with Cat-II DOTS and there is scarcity of data on drug resistance pattern in relapse patients.

Materials and method: This prospective observational study included 128 pa- tients of Cat-II relapse. Detailed history of chemotheraphy was recorded and sputum was sent for mycobacterial culture and sensitivity before starting Cat II DOTS. Resistance pattern of patient was studied.

Results: 122 out of 128 culture and sensitivity reports were available. 104 (85%) patients were culture positive, 15 (12.09%) were smear positive and culture negative. 3 (2.41%) had contaminated culture. 86 (69.35%) patients had resistance to any drug, of which66 (53.22%) were MDR. 12 (8.7%) were multi-drug resistant. 16 (13.16%) patients were treated previously with DOTS and non-DOTS respectively. History of previous chemotherapy revealed 80 (63%) patients had relapses, 11 (9%) were failures and 37 (29%) were defaulters. 56 (73%) had resistance to any drug and, 42 (54%) were MDR in relapse group. 7 (70%) patients had resistance to any drug in failure group and all were MDR. 57% had resistance to any drug in defaulters and 50% were MDR.

Conclusions: High resistance pattern (53.22%) in Cat II relapse patients, thus patients should not be retreated with Cat-II retreatment regimen but empirically treated with revised line drugs till availability of mycobacterial culture and sensi- tivity reports. There is scarcity of drug resistance data for Cat-II relapses and an urgent need of generating data on relapses so that the policy to treat these patients can be established.

P2645
To study outcome of directly observed treatment shortcourse (DOTS) category-I and category-II relapses when put on re-treatment regimen (Cat-II DOTS)
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Background: Under RNTCP Cat-I and Cat-II relapses are put on retreatment regimen. There is scarcity of data on outcome of these relapses and hence, present study was planned to study the outcome of DOTS Cat I and Cat II relapses when put on retreatment regimen (Cat II DOTS).

Patients and methods: A total 289 relapses (161 cases of Cat-I relapse and 128 of Cat-II relapses) patients were included. 150 cases with history of successful treatment and 2 year follow up without relapse were taken as control. 9 patients were lost to follow up. Cat I and Cat II relapses were treated with retreatment regimen (Cat II). Patients were followed up to see changes in radiological and bacteriological parameters as per RNTCP protocol. Outcome was decided based on smear examination at follow ups at 2, 5 and at end of treatment. Mycobacterium culture and sensitivity (Myco CS) reports were collected and bacteriological characteristics of patients were decided. Outcome was defined as per RNTCP guidelines.

Results: Out of 156 Cat-I relapse patients treated with Cat-II DOTS, successful outcome was achieved in 65.37%. Regimen failed in 26.28% and 5.78% patients defaulted. When Cat-II relapse patients were retreated with Cat-II DOTS, successful outcome was achieved in only 36.28% patients. 56.45% patients failed, 4.83% patients defaulted and 2.42% died.

Conclusions: Treatment of Cat-I relapse with Cat-II can be justified with an expected success rate of 65%. The effectiveness of Cat-II DOTS in Cat-II relapse must be elucidated in large multicentre studies and ideally Cat-II relapses should be empirically put on revised line drugs awaiting results of Myco CS.

P2646
An analysis of mortality among patients with tuberculosis (TB) in Sri Lanka
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Introduction: Sri Lanka has a TB prevalence of 101 and a mortality of 9.2 per 100,000.

Objective: To define characteristics of patients who died during treatment for TB in a unit from Central Sri Lanka.

Method: We retrospectively analysed TB related deaths during 2006 to 2010.
Results: We observed a mean mortality rate of 5.4% (228/4199) for the 5-year period. The lowest rate of 3.2% was in 2010. Of the total deaths, 78.5% were males and 50.4% were above 60 years; 4.3% were below 20 years. Pulmonary TB (PTB) contributed to 75% of the deaths.

Conclusion: Mortality in TB was high among males and retreatment patients.

P2647
A tuberculosis-screening program among HIV-infected patients
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Introduction: Tuberculosis (TB) is still the leading cause of death in HIV-infected patients. Its early detection and treatment is a known priority. In 2008 a tuberculosis-screening program among newly diagnosed HIV patients was implemented in a Central Hospital Infectious Unit. Aim: Evaluate the screening program, addressing compliance, case detection and potentially prevented cases.

Methods: A before-after intervention study was performed. Analyzed all newly diagnosed HIV patients between 2007-2008 (before) and 2009-2010 after the program was implemented. Screening included: symptom inquiry, chest radiography, two-step tuberculin skin test and IGRA. Sputum smear and culture were performed when TB was suspected.

Results: From 2007 to 2010, 152 patients were diagnosed with HIV (88 in 2007-2008, 60 in 2009-2010) 75% men, mean age 38.5 y. The before vs after group: 24 (27.6%) vs 36 (57.1%) were injecting drug users (OR: 3.42, CI95%: 1.73 to 6.77); 35 (40.2%) vs 11 (17.5%) had heterosexual risk (OR: 0.31, CI0.14 to 0.68) and 18 (20.7%) vs 3 (4.7%) homosexual (OR: 0.19; CI0.05 to 0.68); 4 vs 11 patients had a known contact with TB (OR: 4.35, CI: 1.32 to 13.49) and 2 vs 7 a previous history of TB (OR: 28.1, CI: 1.06 to 26.33). Screening for TB was done in 69 patients, 21 (32.4%) in the first and 48 (75%) in the second period. LTBI was diagnosed in 3 vs 11 patients (OR: 5.88, CI: 1.57 to 22.06) and active TB was found in 11 vs 21 patients (OR: 3.42, CI:1.51 to 7.76).

Conclusions: The screening program allowed the early identification of more cases of active TB and LTBI. Screening compliance increased, but there were still 25% of HIV patients in the second period that failed screening. Strategies to increase this compliance must be found.

P2648
Unusual association of tuberculosis with schistosomiasis and tuberculosis with sporotrichosis
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Introduction: Tuberculosis is an infectious disease that causes currently nearly 2 million deaths worldwide. More than 200,000 of these occur in patients co-infected with HIV. There are about 700,000 new cases a year, and we found the presence of two cases with atypical association of schistosomiasis and sporotrichosis.

Objective: To report our experience with concomitant infection tuberculosis with schistosomiasis and sporotrichosis.

Method: Cases study of patients infected with tuberculosis in the Hospital of the UNICAMP-Campinas, Brazil.

Results: We found the case of man, 55 years, alcoholic, with pleural effusion for about a year. Thoracocentesis resulted in exudate and ADA= 66 U/L. Chest CT showed mediastinal lymphadenopathy. Result of culture of lymph node removed by mediastinoscopy was positive to Mycobacterium tuberculosis and Sporothrix schenckii. The other case is a 32 years old, male, with a history of fever and weight loss with chest x-ray opacity in the left apex. Chest CT showed a mass in right upper lobe permeated by a tree in bud and mediastinal lymphadenopathy. He underwent lobectomy that showed the presence of Schistosoma mansoni and Mycobacterium tuberculosis in parenchyma, pleura and lymph nodes.

Conclusion: Tuberculosis can be associated to other diseases even in HIV-negative patients, including simulating lung cancer.

280. Risk assessment for tuberculosis

P2649
Within-subject variability of tuberculosis immune responses in health care workers
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Background: Although IFN-γ release assays (IGRAs) are increasingly used for periodic tuberculosis (TB) screening of health care workers (HCWs), data regarding the interpretation of IGRA results in serial testing is scare.

Objective: To evaluate the within-subject variability of two commercial IGRAs, Quantiferon®-TB Gold In-Tube (QFT) and T-SPOT® TB (T-SPOT). Methods: Thirty-four immunocompetent German HCWs (age ≥42 ± 10 y, 79% female) without recent TB exposure or other individual risk factors were repeatedly tested with both IGRAs in weekly intervals over a four-week period.

Results: According to the manufacturers’ predefined dichotomous cut-offs (10% (29.4%) and 3% (8.8%) of the 34 subjects had divergent overall trends with the QFT and the T-SPOT, respectively (p<0.001). The QFT showed 4 unstable conversions (11.8%) and 6 reversions (17.6%), while the T-SPOT showed no conversion and 3 reversions (8.8%). The proportion of concordantly negative IGRA results increased over time. Changes of ±0.70% (QFT) and ±3.2% (T-SPOT) from the mean log IFN-γ response accounted for 95% of the within-subject variability, respectively.

IGRA positivity, discordance and agreement

<table>
<thead>
<tr>
<th>Visit (day)</th>
<th>Subjects</th>
<th>Positive QFT</th>
<th>Positive T-SPOT</th>
<th>Discordant IGRAs</th>
<th>Agreement Kappa</th>
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<tr>
<td>1 (0)</td>
<td>34</td>
<td>11 (32.4)</td>
<td>9 (26.5)</td>
<td>8 (23.5)</td>
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</tr>
<tr>
<td>2 (7)</td>
<td>34</td>
<td>11 (32.4)</td>
<td>9 (26.5)</td>
<td>6 (17.6)</td>
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</tr>
<tr>
<td>3 (14)</td>
<td>29</td>
<td>6 (17.6)</td>
<td>6 (17.6)</td>
<td>2 (5.9)</td>
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</tr>
<tr>
<td>4 (21)</td>
<td>30</td>
<td>4 (13.8)</td>
<td>4 (13.8)</td>
<td>2 (5.9)</td>
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</tr>
<tr>
<td>5 (28)</td>
<td>26</td>
<td>4 (11.8)</td>
<td>3 (8.8)</td>
<td>1 (2.9)</td>
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<tr>
<td>Total</td>
<td>153</td>
<td>36 (23.2)</td>
<td>31 (19.7)</td>
<td>19 (12.4)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Conclusions: We observed considerable variability with both IGRAs and a tendency towards regression of IGRA results over a 4-week period, which should be considered when interpreting repeated IGRA results.

P2650
Conversion and reversion rates in serial examination in German healthcare worker with the interferon-gamma release assay
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Background: Data concerning conversion and reversion rates in serial testing of healthcare workers (HCWs) is rare. There is no consensus to date on how to define and interpret IGRA conversions and reversions. We, therefore analyzed conversion and reversion rates when conducting serial testing of HCWs.

Methods: The study population comprises 426 HCWs from German hospitals, all of whom participated in routine occupational safety and health tuberculosis (TB) screening between January 2007 and October 2010. The QuantiFERON-TB® Gold In-Tube (QFT) assay was used. Different definitions for conversion and reversion were used and risk-related rates calculated.

Results: The first and second QFTs were positive in 8.7% (n=37) of the HCWs,
each. The highest conversion and reversion rates were 3.8% (n=16) and 43.4% (n=23) respectively were observed with the least stringent definition of negative to positive. An uncertainty zone of <0.2 to >0.7 IU/ml gave the lowest conversion rate of 6.6% and a reversion rate of 19.4%. With regards to the different workplaces, we observed a conversion rate of 5.8% in the high risk group, of 4.1% in the moderate risk group and 1.4% in the low risk group from. The highest reversion rate was found in the low risk group (8.5%). However, the differences were not statistically significant.

Conclusion: Our data suggests that HCWs working on wards with a high risk of TB-infection have higher rates of conversions compared to the low risk group and the use of an uncertainty zone of <0.2 to >0.7 IU/ml around the cut-off when conducting serial testing with the QFT.

P2651
Specificity and negative predictive value of the Quantiferon-TB®-Gold In Tube testing on trainees in healthcare settings
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Evidence is growing of high sensitivity and specificity of the interferon-gamma release assays (IGRA) for the detection of latent TB infection. A further question is that of the reliability of their negative results. A few studies have evaluated the outcome of Healthcare workers and trainees with negative IGRA results over time. We analysed the specificity and the negative predictive value (NPV) of the Quantiferon-TB Gold In Tube (QFT) in trainees in healthcare settings.

Methods: A cohort of trainees at the Vivantes healthcare training institute in Berlin established between October 2008 and July 2010 was tested with the QFT at the beginning and after the first year of training.

Results: The study population comprised 194 trainees. Two trainees were excluded from the specificity analysis: one due to indeterminate QFT-IT result and one following a history of TB. Of the 192 trainees at baseline, 153 were still in training. At the beginning of training two trainees were QFT positive (1%). The specificity was estimated as 99%. 151 trainees showed persistently negative QFT results. One trainee was QFT positive during the follow-up. One conversion occurred in one case and one reversion occurred. The NPV in this healthy trainee group was 99.3%.

Conclusion: Our data confirms the findings of a recent meta-analysis (1). This analysis determined a specificity of 99.4% in individuals belonging to low risk groups. The high specificity and the good NPV support the use of QFT for serial testing of HCWs.

References:

P2652
Prevalence of LTBI using IGRA and TST in a cohort of healthcare trainees from India
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Objectives: Estimate the prevalence of LTBI among health professional trainees at a referral hospital in India, using Tuberculin skin test (TST) and Quantiferon TB Gold In-tube (QFT).

Methods: From November 2009 to February 2011, students in health professional programs (except medical and nursing students) were approached for consent. In addition to a detailed questionnaire on TB exposure, participants underwent TST (10 mm) and the QFT-GIT (0.35 IU/ml).

Results: 164 students completed testing. Mean age was 21.5 yrs, 48.8% were female and 59.15% had BCG. Mean time in health care was 11.5 months, and 21.6% recalled contact with PTB cases. Seventy-nine (48.2%, 95%CI: 40.3-56.1%) were positive by TST, and 85 (46.7%, 95% CI: 40.3-53.0%) were positive by QFT. In a cohort of nursing students from the same institution, prevalence was estimated at 21.6% (TST) and 17.04% (QFT), thus lower than the health professional cohort. Possible explanations include a higher proportion of male students compared with nursing, also present cohort were less likely to own a car or house as compared with nursing students, suggesting lower SES. Multivariate logistic regression showed age was associated with QFT positivity but not TST (OR=1.24, 95%CI: 1.01-1.52).

Conclusion: LTBI is common among health professional trainees in India; however, risk factors appear to be better correlated with QFT.

P2653
Evaluation of latent tuberculosis infection in health care workers by Quantiferon-TB Gold test and tuberculin skin test
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Introduction: It is estimated one third of the world population is infected by mycobacterium tuberculosis (TB) and the risk factor of TB infection is contacting with TB patients.

Aim: The aim of this study was to evaluate the parameters affecting the tuberculin skin test and Quantiferon-TB Gold tests and the results of both tests used in health care workers for confirming latent tuberculosis infection (LTBI).

Method: 94 health care workers who work in Yedikule Chest Diseases and Surgery Hospital participated to this study. The demographic characteristics of cases, working hours and the number of BCG scar were recorded. Tuberculin skin test were applied to all patients and Quantiferon levels were measured.

Results: The TST and QFT-G positivities had similar dispersion in gender groups and work types. There were a statistically significant relation between the levels of QFT with work times and ages of all participants. It was determined that there was a statistically significant relationship between positivity of QFT with TST positivities and QFT enduration diameters.

Conclusion: In this study the findings indicated that QTF is very useful in determining and following LTBI as a confirming test for healthcare workers who have close and longterm contact with tuberculosis patients and whose TST tests were positive.

P2654
Serial testing using IGRA in a cohort of Indian nursing students
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Objectives: Evaluate how continuous Interferon gamma response varies across and within individuals over time in nursing students at a tertiary care hospital in Southern India upon annual screening for LTBI using QFT-GIT.

Methods: Students were approached to participate in a longitudinal study. In addition to history, clinical log books provided detailed information on potential TB exposure prior to baseline, and between annual testing. Students underwent QFT-GIT testing in 2008, 2009 and 2010.

Results: 125 nursing students completed QFT testing at 2-3 points for a total of 311 observations. We present a trajectory plot of continuous IFN-gamma across time for each participant.

There exists a high degree of correlation among observations from the same individual (ICC=0.55). To account for the correlation within individuals over time, we used linear mixed models to estimate a subject specific random effects model. We found IFN-gamma results to be negatively associated with successive visits (<0.09) suggesting responses may decline over time. However, this effect was small and not statistically significant. We also identified a small random effect for student (variance = 1.76) after accounting for known LTBI risk factors and TB exposure, suggesting there may be unknown factors contributing to differences in baseline IFN-gamma response across students.

P2655
Tuberculosis screening program using the Quantiferon-TB Gold test and chest computed tomography for healthcare workers accidentally exposed to patients with tuberculosis
Takashi Hiramu, Koschi Hagiwara, Minoru Kanazawa. Respiratory Medicine, Saitama Medical University, Morohongo, Moroyama, Saitama, Japan

Health-care associated transmission of TB is a serious issue. Health care workers (HCWs) have been reported to show high incidences of TB. Periodical screenings and as-needed screenings for HCWs are important. We integrated chest CTs and
the QFT-G test in our TB screening program for HCWs. First, contacts were tested using the QFT-G test. Second, the HCWs positive for the QFT-G test were identified and classified as having TB disease, LTBI, or old TB. Finally, the HCWs with TB disease were treated with a multi-drug regimen, while HCWs with LTBI were treated with INH monotherapy.

Between April 2005 and April 2010, 11 patients who had not been diagnosed with TB disease were found to have TB disease during hospitalization. A total of 512 close contacts and high-risk contacts were identified, who underwent the TB screening program. Out of them, 34 (6.46%) showed positive result for the QFT-G test, whereas 478 (93.54%) showed negative results. Of the 34 QFT-G positive HCWs, 4 had CT findings compatible with TB disease and received multidrug treatment. The chest CT for 24 showed no findings suggestive of TB disease; these HCWs received INH for 6 months. All HCWs who received treatment completed their regimens without any adverse effects. The TB screening program integrating CT and the QFT-G test was safe and feasible (J Hosp Infect in press).

P2656
The additional diagnostic value of interferon gamma release assay to the tuberculin skin test in Greek health care workers (a preliminary study).
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Introduction: Health care workers (HCWs) are at increased risk of Mycobacterium tuberculosis infection. The tuberculin skin test (TST) can be positive (among others) after vaccination with bacille Calmette-Guérin (BCG) creating confusion in countries where this is still compulsory, like Greece. Interferon gamma release assays (IGRAs) are used to solve this problem since they are more specific than TST and usually do not become positive after BCG vaccination.

Aims and objectives: This is a preliminary study aiming to evaluate the additional diagnostic value of QuantiFERON-TB Gold In-Tube (QFT-GT) to the tuberculin skin test (TST) in Greek HCWs.

Methods: A cross-sectional study of TST and QFT-GT was carried out among 275 immuno-competent HCWs at a 900-bed Greek tertiary referral University Hospital. TST was performed on all participants, while QFT-GT was performed in all subjects with TST ≥ 10 mm. Results: Among the 275 study subjects, 124 (45.1%) had TST indurations of ≥10 mm, 96 of them were BCG vaccinated. None had clinical or radiologic evidence of active tuberculosis. From these 124 HCWs, 69 (age 20-67, mean 48.2) agreed to have the QFT-GT test which was positive in only 9/69 (13%).

Conclusion: Based on IGRA’s results, in the majority of Greek HCWs of our study, positive TST was not due to latent tuberculosis infection but to previous BCG vaccination or other unidentified reasons, like exposure to non-tuberculous mycobacteria. This is in agreement with previous study of our Department in a younger age group of Greek Army recruits (S. Katsenos et al. Int J Tuberc Lung Dis 14(5):545-550).

P2657
Concordance between IGRA and TST in a cohort of health professional trainees from India
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1Pulmonary Medicine, Christian Medical College, Vellore, Tamil Nadu, India; 2Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, QC, Canada.

Objectives: To estimate the concordance between the Tuberculin skin test (TST) and QuantiFeron TB Gold In-tube, (QFT) among health professional trainees at a referral hospital in India, and to evaluate risk factors associated with discordant results.

Methods: From November 2009 to February 2011, students registered in various health professional programs (with the exception of medical and nursing students) were approached to participate. In addition to a questionnaire on TB exposure, participants underwent TST (10 mm cutoff) and the QFT/GIT (0.35 IU/ml cut off).

Results: 164 students completed. Mean age was 21.5 yrs (Range: 17-34), 48.8% were female and 59.1% had BCG scars. Mean time in health care work was 11.5 months, and 21.6% recalled direct contact with PTB. Prevalence of LTBI by TST or QFT was 48.2% and 23.2% respectively. Agreement between tests was 71.3% (kappa=0.415). The predominant discordance was TST+/QFT- (43/164, 26.2%). Using multivariable logistic regression we evaluated whether discordant results were associated with any particular risk factors, including: age, sex, education, family income, time in health care setting, days spent in high risk wards, performing high risk procedures, pre-existing medical illness, BCG, and known TB exposure. No factors were associated with discordant results, however, age was associated with concordant positives (OR=1.27, 95%CI: 1.03-1.59), and higher family income was protective (OR=0.67, 95%CI:0.45-0.99).

Conclusions: There was fair to weak agreement between TST and QFT in this population. Concordant positives were associated with older age, and lower family income. Discordant results were not associated with any known risk factors.

P2658
IGRA testing correlation with clinical and laboratory parameters in patients with tuberculosis
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Background: IGRA test (QuantiFeron-TB-Gold in-tube test, further referred as QFT) is based on ELISA method for interferon gamma evaluation created by antigen specific T-lymfocytes. QFT has become a part of complex tuberculosis diagnosis.

Aims and objectives: QFT outcomes comparison with other diagnostic methods in patients with tuberculosis and assessment of malnutrition and immunity system influence on QFT outcomes.

Methods: In a group of 62 patients treated in our clinic for tuberculosis in 2010, we compared the QFT results with tuberculin skin test (TST), PCR, smear and culture. The effect of malnutrition and lymphopenia on possible false QFT negativity was studied as well. Non-parametric Mann-Whitney rank test was used for comparing the mean TST value with QFT and in other parameters. Chi-square test was used in frequency tables.

Results: Statistically significant correlation between QFT positivity and TST negativity, PCR positivity and culture positivity was demonstrated. Statistical significance has not been proven neither between QFT outcomes and microscopic diagnosis nor the effect of malnutrition or lymphopenia on possible false QFT negativity was proven.

P2659
Useful of Quantiferon G in managing solitary pulmonary nodule of less than 3 cm
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Medicine, Bangkok Hospital, Bangkok, Thailand

Introduction: Development of new tools for the rapid diagnosis of tuberculosis is a priority. There are few data from high burden countries on the utility of Quantiferon G for the rapid diagnosis of solitary pulmonary nodule.

Material and methods: We evaluated the utility of Quantiferon G in 30 patients with solitary pulmonary nodule which was less than 3 cm. All were Thai people, and all got BCG vaccine. Bronchoscopy with Autofluorescence was done, bronchial washing was sent for AFB stain, TB culture, PCR-TB and cytology. Tuberculosis test was also performed. Results: Tuberculosis test was positive in 16 patients (53%), Quantiferon G was positive in 19 patients (63%) and PCR-TB was positive in 2 patients (6.7%). Those with positive Quantiferon G were treated with anti tuberculosis drugs for 9 months, all showed satisfactory response. Among those with negative Quantiferon G, 1 year follow up was provided; one turned to be Mycobacterium avium intracellulare, another one developed adenocarcinoma.

Conclusion: Quantiferon G may provide additional useful tool in making decision in managing solitary pulmonary nodule in countries with high incidence of tuberculosis.
P2660
T spot TB - Changing trends and resource implications for trusts
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Introduction: The diagnosis of TB has been revolutionised by Gamma interferon testing with the advantage of being more specific and sensitive in detecting both active and latent TB. East Kent Hospitals NHS Trust is a large trust serving a population of 700,000. This study outlines our experience and in particular focuses on the resource implications as usage of biological agents increases.

Methods: All samples assayed over a twelve month period were included in the study. Data, including the demographics of the patients, indication for the test and the result, was collected. The data was analysed.

Results: A total of 491 samples were sent for analysis within the study period. There was an equal gender distribution (M:F = 221:270) and the median age was 53.02.

Table 1. Reason for requesting T spot T.

<table>
<thead>
<tr>
<th>TB diagnosis</th>
<th>TB Screening</th>
<th>Pre-biologics</th>
<th>Reason not specified</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>77</td>
<td>156</td>
<td>185</td>
<td>491</td>
</tr>
<tr>
<td>14.47%</td>
<td>15.68%</td>
<td>31.77%</td>
<td>37.68%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conclusion: T spot TB provides a highly sensitive and specific way of detecting active or latent TB. Almost a third of the requests are to assess TB status prior to the introduction of biological agents. This will have a major impact on resources with the increased usage of biologicals, something that needs to be borne in mind whilst developing this service.

P2661
Clinical utility of the interferon-gamma for the diagnosis of active pulmonary tuberculosis
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Introduction: A rapid diagnosis of TB is crucial not only for patients, but also for TB control in the community. Currently, T-cell based interferon gamma release assays (IGRA) are acknowledged as the best methods available for the screening of latent tuberculosis infection (LTBI) and also as aid for the diagnosis of active tuberculosis (TB). The performance of these diagnostic tests has not been evaluated in Serbia.

Aim: To compare the sensitivity of Quantiferon-TB Gold In-tube test (QFT), tuberculin skin test (TST) and acid-fast staining of sputa in patients with culture confirmed active pulmonary TB (PTB).

Methods: The sensitivities were evaluated in 70 HIV negative patients with culture confirmed Mycobacterium tuberculosis infection. The sputum culture result was used as a gold standard. TST results were analysed at 5, 10 and 15mm cut-offs. QFT test was interpreted following the manufacturer’s criteria.

Results: Sensitivities of the TST using a 5, 10 and 15mm of cut-offs were 55.7%, 51.4%, 45.7% respectively. Sensitivity of QFT (68.6%) was higher than that for all the TST sensitivities. The overall agreement between TST (all cut-offs) and QFT was poor. Sensitivity of the acid-fast staining of sputa was 75.7%.

Conclusion: Although findings have revealed a generally low sensitivity of the QFT, our opinion is that QFT can be used as adjunct diagnostic technique for active TB disease.

P2662
Unfavorable factors associated with false negative results of interferon-gamma release assay for tuberculosis
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Imperfect sensitivity of interferon-gamma release assay (IGRA) is a potential problem to detect tuberculous infection. We comprehensively investigated factors that can lead to false negativity of IGRA, regarding active tuberculosis as a surrogate. In total, 543 patients with new smear-positive pulmonary tuberculosis were tested. At the time of diagnosis, peripheral blood was collected and IGRA (QuantiFERON-TB Gold In-Tube®, Cellestis, Victoria, Australia) was performed. Clinical and epidemiological information of the host and pathogen was collected together. Factors negatively influencing IGRA results were evaluated using logistic regression model.

Age ≥80 years old, body mass index <18.5 and the extensive infiltrates on chest X-ray showed significant associations with IGRA negativity (OR = 8.47 [95% CI, 1.53–46.84], 3.46 [95% CI, 1.14–10.49], and 3.07 [95% CI, 1.18–7.97], respectively), whereas HIV co-infection was rather associated with indeterminate results (OR = 23.30 [95% CI, 4.28–126.82], respectively). Having HLA-DQB1*0701 allele was also associated with IGRA negativity; the number of the HLA allele that the patients possess correlated inversely with concentrations of interferon-gamma induced by M. tuberculosis-specific antigens (heterozygotes; 2.08 IU/ml [interquartile range, 0.79–4.64] and homozygotes; 0.15 IU/ml [0.06–0.26], respectively; P = 0.0064).

A variety of factors including an HLA allele affect false negativity of IGRA. Assessment of these factors in tested populations would contribute to a secure and reliable interpretation of IGRA results.

P2663
The influence of a high negative control on the interpretation of Quantiferon Gold in Tube (QFN) results
William Ricketts, Graham Bothamley. Respiratory Medicine, Homerton University Hospital, London, United Kingdom

Introduction: The QFN result is a composite of a nil control, a mitogen positive control and a test sample (TB Ag) utilising ESAT-6, CFP-10 and TB 7.7 antigens. The result is defined as TB Ag minus nil control (positive ≥ 0.35 IU/ml). A strongly positive nil control (> 8 IU/ml) or failure of the positive control are defined as indeterminate results. We were concerned that high values obtained after antigen stimulation might be significant.

Method: All patients tested by QFT-GIT between 31/3/10 and 28/1/11 (=n=651) had the raw data from their test reviewed. Clinical diagnosis was examined in all those with a TB Ag result >0.35 IU/ml with a nil control high enough to bring the net result to <0.35 IU/ml or an indeterminate result.

Results: There were 39 (6%) instances of a net negative result despite a response to antigen, including four cases of active TB (4.7% of TB cases). Nil control results ranged from 0.1-3.07 IU/ml, with TB Ag levels up to 1.52 IU/ml.

Eight with a negative mitogen response included two cases of active TB, one of whom also had HIV. No cases were defined as indeterminate by virtue of a strongly positive negative control.

Conclusion: Reporting of a net result without a breakdown leaves clinicians vulnerable to missing cases of active TB. Sarcoïdosis, Crohn’s disease and bronchectasis, all diseases associated with polyclonal B cell activation, also appear to spontaneous interferon-gamma release.

P2664
Clinical history and IGRA is unreliable in the diagnosis of tuberculosis
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Aim: To monitor the stages in the diagnosis of tuberculosis (TB) and assess whether early interferon-γ responses can be helpful.

Method: Site – a TB clinic in a high incidence (58 per 100,000) area of London. 25 patients with suspected TB were followed through their diagnostic process. Patients were scored using a modified UCSD Clinical Suspicion of TB tool by two clinicians blinded to the patient’s identity and each other’s scores. Estimated risk of TB was made at four stages in the diagnostic process: with clinical data, TST,
HIV and IGRA (QuantiFERON Gold in Tube) results, after radiology; sputum smear; and blood tests. A decision as to whether to offer treatment was made at stage two and at each stage thereafter.

Results: Clinical history with IGRA was associated with a wide variation in estimated probability of TB (%QR 15-85%). As the diagnostic process progressed, accuracy increased (see figure) and inter-scorer variation decreased. Diagnosis of culture-negative TB was especially problematic. Despite differences between the two scorers there was no difference in the number of patients treated correctly after radiology (69% vs 54% TB; 92% vs 92% not-TB), sputum smear (67% vs 44% TB; 83% vs 92% not-TB) and other blood tests (77% vs 46% TB; 92% vs 92% not-TB).

Conclusion: Clinical history even with IGRA results is unreliable in the diagnosis of TB. New tests for culture-negative TB would be valuable.

P2665 Specificity of IGRA in Japan
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1Department of Mycobacterium Reference and Research, Research Institute of Tuberculosis, Kiyose, Tokyo, Japan; 2Division of Control and Treatment of Infectious Diseases, Chiba University Hospital, Chiba-cho, Chiba, Japan

Objective: The specificity of IGRA with the population being tested. The specificity of T-SPOT® TB (T-SPOT) is generally reported to be lower than that of QuantiFERON® TB Gold In Tube (QFT-GIT). It is likely that studies carried out in developed countries include individuals with latent tuberculosis infection (LTBI). Therefore, we compared the specificities of T-SPOT and QFT-GIT in selected healthy subjects in Japan.

Subjects and methods: Blood samples were taken for both T-SPOT and QFT-GIT from university students who were selected according to stringent inclusion criteria and performed according to the manufacturer’s instructions. Blood samples for T-SPOT were kept overnight at room temperature and treated the next day with T-Cell Xtend prior to PMBC preparation. Blood samples for QFT-GIT were incubated within 16 hours after blood collection.

Results: University students with very low risk factors for TB infection were strictly selected, especially as there is no gold standard for LTBI. If studies do not adhere on plate wells even after intensive washing.

Conclusion: These observations suggested that live lymphocytes adhered on ELISA plate well may produce non-specific reaction, which result in higher IFN-γ values. Therefore, in order to obtain accurate results, QFT-GIT plasma samples after harvesting from QFT-GIT blood collection tubes should be re-centrifuged to spin down live lymphocytes.

P2668 Accuracy of IFN-γ and IP-10 detection for diagnosis of tuberculosis in children
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Objective: Evaluate IP-10 detection for latent tuberculosis infection (LTBI) and active tuberculosis (TB) in children, comparing the results with IFN-γ detection.

Material and methods: IFN-γ released was determined by QuantiFERON-TB Gold In Tube (QFT). IP-10 was retrospectively detected in supernatants by an in-house ELISA and analyzed using preset cut-offs for positive (4.37ng/ml) and indeterminate (3.5ng/ml) IP-10 test result (Ruhwald, Latorre in prep).

Results: 45 pediatric patients were classified in 3 groups:
Group 1: 10 children diagnosed with active TB, with a Mycobacterium tuberculosis positive culture or active clinical TB.
Group 2: 15 children enrolled during LTBI screening studies, with a positive QFN. Group 3: 20 healthy control children, with a negative QFN.

Sensitivities of both IFN-γ and IP-10 assays were 50% (Group 1). Specificity of IP-10 detection was 100% (Group 3). Combining both cytokines the sensitivity improved to 60%, without a compromise of the specificity. Percentage of positive IP-10 responders among children from group 2 was 66.7%. Two children with negative IP-10 assays from this group had QFN positive borderline results. Global concordance between assays was 82% (x=0.624). IP-10 released after specific antigen stimulation in active TB patients was significantly higher than in healthy controls (p<0.007), this was not seen for IFN-γ (p=0.19).

Conclusions: IFN-γ and IP-10 sensitivity is low, but combination of both cytokines increased sensitivity without a compromise of the specificity. Lowering IP-10 and IP-10 cut-offs could improve the sensitivity in children. Concordance between both assays is good. IP-10 could be an alternative marker for LTBI and active TB in children.
281. Extrapulmonary tuberculosis and surgical interventions

P2669
Serum and pleural fluid cytokines in pleural tuberculosis with and without lung parenchyma involvement
Marcia Seiscento 1, Francisco Vargas 1, Roberta Sales 1, Leticia Texeira 1, Juliana Puka 1, Milena Accenio 1, Leila Antongiorgi 1, 2, Pulmonary Division, Pleura Laboratory, Heart Institute (InCor) – University of Sao Paulo Medical School, Sao Paulo, Brazil; 2 LIM 03 – Clinical Laboratory, Pathology Department, University of Sao Paulo Medical School, Sao Paulo, Brazil

Pleural tuberculosis (PT) is frequent form of extrapulmonary disease. In the pleural cavity, activated T lymphocytes produce cytokines in response to the mycobacteria and its antigens. Lung parenchyma can be concomitantly involved in up to 40% of cases.

Objective: To compare serum (S) and pleural fluid (PF) levels of inflammatory mediators in patients with PT in order to verify if lung-associated involvement influences the magnitude of the inflammatory response.

Methods: A prospective study of 39 patients with pleural (20) or pleuropulmonary (19) tuberculosis was conducted. IL-8, VEGF, TNF-α, and TGF-β1 were quantified by ELISA.

Results: The proinflammatory cytokines TNF-α and IL-8 were higher in PF than in S of 5 patients with the pleural form, while only IL-8 was higher in the pleuropulmonary form. Only PF TNF-α was capable to discriminate both forms of TB disease.

Pleural and Serum variables analyzed in patients with pleural and pleuropulmonary tuberculosis

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Pleural TB</th>
<th>Pleurapulmonary TB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF PF</td>
<td>1207 (931-1488)</td>
<td>1509 (966-1196)</td>
<td>0.085</td>
</tr>
<tr>
<td>VEGF S</td>
<td>780 (221-1254)</td>
<td>1190 (507-1975)</td>
<td>0.160</td>
</tr>
<tr>
<td>TNF-α PF</td>
<td>119 (72-233)</td>
<td>420 (155-472)</td>
<td>0.025</td>
</tr>
<tr>
<td>TNF-α S</td>
<td>16 (16-144)</td>
<td>54 (16-843)</td>
<td>0.183</td>
</tr>
<tr>
<td>IL-8 PF</td>
<td>158 (161-1387)</td>
<td>1512 (1281-1885)</td>
<td>0.092</td>
</tr>
<tr>
<td>IL-8 S</td>
<td>31 (31-128)</td>
<td>31 (31-129)</td>
<td>0.496</td>
</tr>
<tr>
<td>TGF-β1 PF</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.955</td>
</tr>
<tr>
<td>TGF-β1 S</td>
<td>492 (396-1088)</td>
<td>653 (426-1011)</td>
<td>0.520</td>
</tr>
<tr>
<td>p</td>
<td>0.013</td>
<td>0.077</td>
<td></td>
</tr>
</tbody>
</table>

PF = Pleural fluid; S = serum.

Conclusion: Although TNF-α levels had been higher in the PF of patients with PT and lung involvement, we suggest its dosage in association with computed tomography in order to identify these patients, since they represent potential source of infection and disease spread.

P2670
The use of ADA liquid level in diagnosis of tuberculous pleurisy in countries with low incidence of tuberculosis
Perlat Kapisyzi, Dhimitraq Argiri, Anila Aiklo, Jeta Beli, Ylli Vakeflliu, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, Faculty of Medicine, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania Lung Diseases, University Hospital Lung Diseases, Tirana, Albania.

The aim: To study the use of cut off values of fluid ADA level in differential diagnosis of tuberculous pleurisy.

Materials and methods: 121 consecutive patients with pleural effusion were prospectively studied. The study included 82 males, 39 females with a mean age of 59.3±17 years. Exudative effusions were classified as malignant pleural effusions, 39 (39.8%), TB pleural effusions, 39 (39.8%), parapneumonic pleural effusions, 20 (20.4%). The photometric method was used.

Results: In tuberculous group the mean of ADA level was 122.4±48.3 UI/L. No patients of age < 35 years had ADA level under 40 U/L. In tuberculous group the mean of ADA level was 122.4±48.3 UI/L. No patients of age < 35 years had ADA level under 40 U/L. The sensitivity of ADA in TB effusions at cut-off > 40 U/L was 89.7%, specificity 28.8%, PPV 54.5%.

P2671
Evaluation of real time polymerase chain reaction in rapid diagnosis of exudative tubercular effusions
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Introduction: Exudative effusions are a common manifestation of tuberculosis. Real time Polymerase Chain Reaction (RT-PCR) has superior sensitivity, specificity, lower contamination and reduction in time to result in comparison to conventional methods.

Aims and objectives: To evaluate the sensitivity of RT-PCR in cases of exudative effusions due to tuberculosis.

Methods: RT-PCR was performed in 153 patients of exudative tubercular effusions. They consisted of 127 pleural effusions, 21 ascitic fluid and 5 pericardial effusions. All patients had positive Mantoux test with high protein and lymphocyte predominance in effusion. The subjects were positive by either ZN staining, Culture for AFB by growth on LJ medium or BACTEC, Interferon γ (INF-γ) or Adenosine Deaminase (ADA).

RT-PCR was performed by detecting amplification reaction for the insert element IS6110 of the Mycobacterium tuberculosis complex (Biotech-QT, Biotools Labs, Spain) using a real-time centrifugal amplification system (Rotorgene-3000, Corbett Research, Australia).

Results: RT-PCR was positive in 134 of the 153 cases of exudative tubercular effusions (Sensitivity 87.6%). It was positive in 114 of 127 cases of pleural effusion (Sensitivity 89.7%), 17 out of 21 cases of ascitic and 3 of the 5 cases of pericardial effusion. The sensitivity of ZN staining was 23.5%. Culture by LJ medium was 33.9% and BACTEC was 51.3%. ADA showed positivity in 144 of 153 cases (Sensitivity 94.4%) and INF-γ showed sensitivity of 83.6%.

Conclusion: Real time PCR is valuable in the diagnosis of exudative tubercular effusions with a sensitivity of 87.6%. The diagnostic efficiency could be increased by combining RT-PCR with ADA or INF-γ.

P2672
Adult thoracic empyema: A comparative analysis of tuberculous and nontuberculous etiology in 75 patients
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Background: Thoracic empyema is a disease of significant morbidity and mortality in the developing world where tuberculosis is a common cause. Clinical outcomes in tuberculous empyema are complicated by fibrocavitary disease and bronchopleural fistula. A prospective study to compare the clinical profiles and outcomes of patients with tuberculous and nontuberculous empyema was performed.

Materials and methods: A prospective study of adult nonsurgical thoracic empyema cases admitted in a teaching hospital in India was performed over a period of 18 months. A comparative analysis of clinical characteristics, treatment modalities, and outcomes of patients with tuberculous and nontuberculous empyema was carried out.

Results: 75 cases of empyema were seen during the study period, of which 46 (61.3%) were of nontuberculous etiology while tuberculosis constituted 29 (38.7%) cases. Among the nontuberculous empyema patients, Staphylococcus aureus (11, 23.9%) was the most frequent pathogen isolated. Tuberculous empyema was more frequent in younger population compared to nontuberculous empyema (mean age of 32.7 years vs. 46.5 years). Duration of illness and mean duration of chest tube drainage were longer (48.7 vs. 23.2 days) in patients with tuberculous empyema. Also the presence of parenchymal lesions and bronchopleural fistula often requiring surgical drainage procedures was more in tuberculous empyema patients.

Conclusion: Tuberculous is a common cause of empyema thoracis in a developing country. Tuberculous empyema differs from nontuberculous empyema in the age profile, clinical presentation, management issues, and has a significantly poorer outcome.
**P2673**

High yield of liquid mycobacterial culture in pleural fluid and tissue
Florian von Groote-Blingdinger1, Kiki Chung2, Corne Rautenbach3, Maurizio Bemasco1, Cornelia Koelega1, Elizabeth Wasserman1, Chris Bullinger1, Andreas Diacos1.

**Method:** We investigated 66 consecutive patients with exudative effusions of suspected inflammatory or infectious nature in a single session and directly compared the yields for a diagnosis of TB of a spot smear and smear, culture pleural fluid ADA and cell count, low volume (5ml) and high volume (100ml) liquid mycobacterial culture and pleural biopsy histology and culture. A final diagnosis of TB was established in 50 patients (75.8%) by histological proof of granuloma-tous inflammation or any positive culture. All TB cultures were performed in an automated liquid culture system (MGIT 960, Becton Dickinson).

**Results:** Available results among these 50 patients indicated the following respective yields:
22/34 (65.7%) for spot smear (sputum positive: 17.1%; culture positive: 61.3%); 44/46 (95.7%) for pleural fluid adenosine deaminase (ADA) ≥ 50 U/l; 32/41 (78%) for ADA ≥ 50 U/l combined with lymphocyte predominance; and 31/46 (67.4%) for pleural fluid MGIT culture (low volume: 56.5%; high volume: 63%; p>0.45).

**Conclusion:** Liquid mycobacterial culture has an exceptionally high yield in both pleural fluid and tissue and should be routinely used.

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**P2674**

Pleural tuberculosis: A study of 46 cases
Besma Hamdi, Chiraz Aichouia, Samef Ferh, Samira Bhamdi, Zied Moatamiri, Sahabbi Daboussi, Ghaya Laaribi, Mounes Khadhraoui, Rzaieg Cheikh.

**Pleural tuberculosis (TB) remains a diagnostic challenge. It is the most frequent extra pulmonary localisation.**

To focus on clinical, radiological, biochemical and histopathological characteristics of pleural TB and the sensitivity of the various diagnostic tests. We studied retrospectively 46 patients in whom pleural TB were diagnosed in our military department. The mean age was 29.8 year (12 to 78 year). 78.2% were male. A retrospective study concerned 117 cases of tuberculous pleurisy in Blida between 2005 and 2009.

**Aims and objectives:** The aim of our study is to clarify the characteristics of the epidemiology, diagnosis, treatments and outcome of pleural tuberculosis and also to clarify the predisposing factors.

**Methods:** Our retrospective study concerned 117 cases of tuberculous pleurisy supported for 05 years from 2005 to 2009 among a total of 764 cases followed for extrapulmonary tuberculosis at the Blida tuberculosis control unit.

**Results:** Our study has assembled 67 men and 50 women with a mean age of 30 years. Comorbidities in number of 7 are represented by 4 cases of metabolic syndrome. The impairment is most often right sided in 57.2% of cases, and bilateral in 11% of cases. The investigations carried out showed a tuberculin allergy in 31.6% of cases. The histology diagnosis was mainly contributing in 42.7% of cases by finding caseofolicial tuberculosis, and in 23.9% of cases by a tuberculoid inflammation. The antibiotic treatment was started in all cases with a favorable outcome to the healing in 50.4% of cases and with sequelae in 45.2% of cases. However, we noted 4 cases of lost sight and one patient transferred for therapeutic monitoring.

**Conclusion:** The management of pleural tuberculosis is correlated by the improvement of diagnostic methods, certainty including pleural biopsy and thoracoscopy.

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**P2675**

Features of diagnostics for exudative pleurisy of tuberculosis etiology
Kazim Mukhamedov1, Avar Muzrabezov1, Sherali Massayev1, Stanislav Kostromin1, Fuzilat Ismailova1, Elmira Khudayberdieva1. 1Faculty of Pathiologics, Tashkent Medical Academy, Tashkent, Uzbekistan; 2Faculty of Preparation of General Practitioners, Tashkent Medical Academy, Tashkent, Uzbekistan.

**Background:** To study the features of diagnosis and therapy for exudative pleurisy of tuberculosis etiology (EPTE).

**Materials and methods:** There analyzed 122 cases with EPTE. Men were 76 (62.3%), women-46 (37.7%), aged between 17 to 69 years. 1-group included 59 (48, 4%) patients who had revealed/or suspected EPTE based on clinical and X-ray data after admitting in out-patient clinic or antituberculous dispensary. 2-group included 63 (51.6%) patients who primarily were hospitalized in general medical network (GMN) clinics and underwent erroneous treatment for different lesions and physiotherapy. The outcome was favourable in all cases. 45,6% of patients developed pleural thickening 6-12 months after beginning of treatment. TB, whatever mucosal and extrathoracic dissemination, remained in 1 of 9 in group C and 3 of 12 in group D, and moderate RPT were reached preferentially the young adults.

**Results:** Focal TB was diagnosed in 55 (45, 1%), infiltrative –34 (27, 9%), disseminated- 11 (9, 0%), pleural TB - in 8 (6,6%), intrathoracic lymphatic nodes - in 14 (11, 5%). Bronchoscopy revealed active specific changes in 34 from 63 examined patients including rough deformed cicatrical changes in 11 patients. Mantoux test was positive in 84 (68, 9%). M.Tuberculosis (MBT) were found in 105 (86,1%). Revolt positive test was revealed in exudates.

**Conclusion:** Exudative pleura diagnostics is a challenge. It should be paid an important place to general medical network doctors’ high concern in regard to TB.

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**P2676**

Advantage of chest tube drainage in tuberculosis pleurisy without active pulmonary tuberculosis
Moon Jun Na, Ji Hye Kim, Yu Mi Lee, Sun Jung Kwon, Ji Woong Son, Eugene Chiu. Department of Internal Medicine, Konuyang University College of Medicine, Daejeon, Republic of Korea.

**Introduction:** Early effective drainage may hasten clearance of pleural effusion and reduce the occurrence of residual pleural thickening (RPT) in patients with symptomatic loculated tuberculous pleurisy (TBP).

**Objectives:** The effects of a large-bore chest tube drainage (CTD) with a small-bore percutaneous drainage (PCD) or no-drainage group in TBP were compared.

**Methods:** We reviewed retrospectively the records of TBP patients without active pulmonary TB lesion that diagnosed by thorascopic biopsy or high ADA of pleural fluid from 2005, January to 2010. December. All patients were treated with anti-TB medication over 6 months. We divided into 4 groups (group A: no-drainage (n=7), group B: CTD without loculation (n=10), group C: CTD with loculation (n=9), group D: PCD with loculation (n=12)). We compared the RPT, days of hospitalization and tube inserted between group A vs B, and group C vs D.

**Results:** In non-loculated TBP patients, mild RPT were remained in 1 of 7 in group A and none of 10 in group B. In loculated TBP patients, mild RPT were remained in 1 of 9 in group C and 3 of 12 in group D, and moderate RPT were found in only group D (2 in 12). Days of hospitalization were 8.7±1.5 in group A vs 10.6±3.3 in group B, and 16.7±10.2 in group C vs 10.4±6.9 in group D. Days of tube inserted were 6.8±2.5 in group C vs 4.6±2.8 in group D.

**Conclusion:** Although using a large-bore CTD needs longer days of admission and tubing, CTD was more effective than PCD in RPT reduction of loculated TBP. CTD was not advantageous to drainage without diagnostic thorascoscopy in RPT reduction of non-loculated TBP, in addition to definite diagnosis by thorascopic biopsy.

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**P2677**

Pleural tuberculosis: A retrospective study in the tuberculosis control unit of unit of Blida between 2005 and 2009.
Lotfi Nacef, Oma Saaghi. Thoracic Diseases Department, E.P.H Blida, Blida, Algeria Thoracic Diseases Department, E.P.H Blida, Blida, Algeria.

**Introduction:** Pleural tuberculosis is among the most common sites of extrapulmonary tuberculosis, which represent 30% of all tuberculosis cases in Algeria. She reached preferentially the young adults.

**Aims and objectives:** The aim of our study is to clarify the characteristics of the epidemiology, diagnosis, treatments and outcome of pleural tuberculosis and also to clarify the predisposing factors.

**Methods:** Our retrospective study concerned 117 cases of tuberculous pleurisy supported for 05 years from 2005 to 2009 among a total of 764 cases followed for extrapulmonary tuberculosis at the Blida tuberculosis control unit.

**Results:** Our study has assembled 67 men and 50 women with a mean age of 30 years. Comorbidities in number of 7 are represented by 4 cases of metabolic syndrome. The impairment is most often right sided in 57.2% of cases, and bilateral in 11% of cases. The investigations carried out showed a tuberculin allergy in 31.6% of cases. The histology diagnosis was mainly contributing in 42.7% of cases by finding caseofolicial tuberculosis, and in 23.9% of cases by a tuberculoid inflammation. The antibiotic treatment was started in all cases with a favorable outcome to the healing in 50.4% of cases and with sequelae in 45.2% of cases. However, we noted 4 cases of lost sight and one patient transferred for therapeutic monitoring.

**Conclusion:** The management of pleural tuberculosis is correlated by the improvement of diagnostic methods, certainty including pleural biopsy and thoracoscopy.

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**P2678**

Specific pulmonary lesion in patients with tubercular spondylitis (TS)
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120 patients with active pulmonary tuberculosis (PT) and diagnosis of TS were studied. It was the patients at the age from 18 to 72 years old. The patients were examined due to complaints of spinal pain. These were mostly the lesions of...
Tuberculous spondylitis as a mirror of a severe epidemic situation
Ekaterina Kulhavchenya, Eugeniu Koveshenkova. Urological, Research TB Institute, Novosibirsk, Russian Federation

Introduction: Tuberculosis of bone and joints (BJTB) is one of the leading forms among extrapulmonary TB. The aim was to estimate a spectrum of extrapulmonary TB in Novosibirsk – the capital of Siberia, and reveal a tendency in BJTB.

Material and methods: Statistical reports were estimated, also 177 patients with BJTB were enrolled in study.

Results: Among all cohort of extrapulmonary TB female patients was 50.9% and male patients - 49.1%, but in BJTB ration female:male was 1:2.

The share of BJTB in extrapulmonary TB increased from 3.3% in 1992 up to 28.0% in 2006, and reached 48.6% in 2008. Among BJTB tuberculous spondylitis prevails (72.2%), mostly complicated by neurological disorders and paravertebral abscesses and combined with TB of other organs. Nevertheless in 65.5% only 2 vertebras were involve in TB process. In 17.2 debut of disease was acute or sub-acute, but diagnostic took 14.1 months on average. One of the main reason is poor alertness physician for tuberculosis and late X-ray examination. Typical X-ray picture of TB spondylitis is shown on figure 1.

Poverty, unemployment and alcoholism resulted in poor efficiency of the therapy in 45.7% patients. Patients endomorphic body type in 8.5 times more likely to have delayed consolidation.

Conclusion: In regions with severe epidemic situation it is necessary always to keep in the mind TB in patients with back pain and make X-ray examination as soon as possible.

P2680
Tuberculous myotic aneurysm of aorta: A rare complication
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39 year old male was started on antituberculous treatment based on symptoms and miliary shadows on chest x-ray. 2 months later he had persistent abdominal pain. Abdominal examination revealed a pulsatile palpable mass with brux. Ultrasound &CT abdomen confirmed aneurysmal dilatation of aorta from hiatus to bifurcation with infra renal involvement. No leak or dissection.

Surgical exploration revealed aneurysm with areas of impending rupture, clots & caseous material. Endoaneurysmal graft repair surgery was done. Clot was teem-
ing with AFB. Postoperatively patient had paraplegia due to ischemic myelopa-thy.

Tuberculous mycotic aneurysm of aorta is a rare complication with poor prognosis. Less than 50 cases have been reported. Combined medical & surgical therapy is advised.

P2683

Tuberculosis in residual pleural cavity after segmental pulmonary resections and its surgical treatment
Tulkin Kariev, Sunnatilla Abulkasimov, Sherdzod Rahmonov. Thoracic Surgery Department, National Centre of Phtisiology and Pulmonology, Tashkent, Uzbekistan

Repeated operations on account of development of tuberculosis in the residual pleural cavity after segmental resections were performed in 54 patients (males – 35, females -19) in ages between 17 and 46. Residual cavity due to incompletely lung spread developed on the left in upper segments of thoracic cage in 30 patients, on the right – in 24 patients after segmental (9), combined resections (16), lobectomy (26) and bilobectomy (3) on account of fibrous-cavernous tuberculosis. Tuberculosis in residual cavity was diagnosed in 6 months - 1 year after the operations in 28 patients, in 3 years – in 19, in 4-5 years – in 7. Bacteria excretion in sputum was detected in 41 patients (75.9%). After pre-operative chemotherapy and general treatment, lobectomy was performed in 1 patient, pulmonectomy - in 15, thoracoplasty with myoplasty of residual cavity – in 38. Good effectiveness of repeated operations stated in 43 patients (79.6%), unsatisfactory results due to the exacerbation of bronchoalveolar fistula and pleural empyema - in 7 (12.9%). Lethality in 4 patients (7.5%) occurred from the progress of bronchial fistula, plural empyema and pulmonary tuberculosis.

Conclusion: Tuberculosis in residual pleural cavity after segmental pulmonary resections is a heavy pulmonary and pleur al pathology characterized by chronic course. Repeated operations – pulmonectomy and thoracoplasty with myoplasty of the residual cavity – are highly effective and allow healing 82.1% of patients.

P2684

Asymptomatic oesophageal and bony involvement in an HIV-negative female with pulmonary TB
Rawya Ahmed1, Simon Allen 2, Parthipan Kanthapillai1.

Tulkun Kariev, Sunnatilla Abulkasimov, Akrat Giresash. Thoracic Surgery Department, National Centre of Phtisiology and Pulmonology, Tashkent, Uzbekistan

A 44 year-old lady of Afro-Caribbean origin presented with a 4-months history of productive cough, night sweats and weight loss. There were no other symptoms or significant medical history. Chest auscultation revealed right-sided apical bronchial breathing and coarse crepitations mid to lower zones. Chest radiography confirmed apical cavitation and right-sided consolidation. Sputum microscopy and molecular polymerase chain reaction test showed fully sensitive mycobacterium tuberculosis (TB). Thoracic computed tomography revealed a pneumomediastinum, oesophageal perforation and gaseous permeative infiltration of T1-T3 vertebrae.

A human immunodeficiency virus (HIV) screen was negative. Oesophageagastrodrodenoscopy was normal apart from a 2cm punched out lesion at 23cm of the oesophagus. Quadruple anti-TB therapy and enteral feeding were established via a percutaneous gastrostomy tube to avoid mediastinitis and allow healing. Clinically occult oesophageal perforation and bony involvement in the absence of HIV infection or miliary TB has not been previously described. The mechanism of this is unclear, but may involve a coseating mediastinal lymph node.

P2685

Surgical treatment of first found pulmonary tuberculosis at ineffectiveness of DOTS therapy
Tulkin Kariev, Sunnatilla Abulkasimov, Akrat Giresash. Thoracic Surgery Department, National Centre of Phtisiology and Pulmonology, Tashkent, Uzbekistan

Surgeries were performed in 43 patients (males-27, females-22) in ages between 18-53 years old. All the patients had first found destructive tuberculosis of lungs, and ineffectiveness of DOTS therapy was stated in them. During 2-3 months, 23 patients received chemotherapy in hospital (isoniazid, rifampycin, pyrazinamide, ethambutol or streptomycin) and ambulant therapy (isoniazid and rifampycin) under the 1st category of DOTS during 4-6 months. After diagnosing pulmonary tuberculosis, the treatment according to the 1st DOTS category (intensive phase-2-3 months, supporting phase 4-6 months) was received by 20 patients in the first phase. Because of ineffectiveness of chemotherapy, the treatment was continued under the 2nd DOTS category intensive phase chemotherapy with 5 preparations (H, R, Z, E and S) during 3-4 months and ambulant phase (isoniazid, rifampycin, ethambutol) during 6-8 months. Ineffectiveness of DOTS based chemotherapy-continuing bacteria excretion, presence of pulmonary destruction served as indication to surgical treatment. Segmental pulmonary resection was carried out in 7 patients, lobectomy in 12, pulmonectomy in 24. Good clinical effect of performed operations was reached in 40 patients (93.0%). Unsatisfactory results (bronchial fistula and plural empyema) were stated in 2 patients (4.7%). Lethality in 1 patient (2.3%) was caused by the progress of pulmonary tuberculosis and pleural empyema.

Conclusion: When DOTS chemotherapy is ineffective, surgical treatment of first found destructive pulmonary tuberculosis is an important and effective final stage of complex therapy that prevents transition of patients into the group of chronic patients.

P2686

Method of treatment of destructive tuberculosis of single lung with extensively drug resistant mycobacteria tuberculosis
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Treatment of patients with TB with total defeat of one lung and presence of destruction in the other, with a constant allocation of extensively drug resistant Myc. tuberculosis (XDR MBT), remains extremely weak. Under these conditions, the role of surgical and endoscopic therapies is rising.

Objective: To improve treatment of patients with fibrous-cavernous tuberculosis of a single lung with XDR MBT due to valvular lung volume reduction (VLVR) and local extrapulmonary thoracoplastics.

Material and methods: The treatment was performed in 13 patients (10 men, 3 women) of fibrous-cavernous tuberculosis of a single lung with XDR MBT. The patients’ age ranged from 30 to 54 years. Disease duration ranged from a half to 8 years, all patients were smear.

The essence of the proposed method is to use endobronchial non-return valve. Valve ensures the smooth discharge of air, sputum, bronchial content in the ex- hale, and cough. Inverse of air in the lung lesions did not occur. Thus, gradually hyperventilation was being reached, until atelectasis of lung tissue. VLVR performed during treatment with reserve anti-TB drugs. In 6 patients with VLVR was supplemented extrapulmonary thoracoplastics.

Results: Time that valve spent in the bronchus depended on the rate of cavity closure and cessation of bacteria and ranged from 7 to 274 days. Abacillation was achieved in 100% of patients, the cavity was closed in 76.9% of patients.

Conclusions: The proposed method of treatment of patients with tuberculosis enables us to reduce lung cavity and reach abacillation patients with XDR MBT in the absence of the effect of chemotherapy with reserve anti-TB drugs and a high risk of single lung resection.

P2687

Artificial therapeutic pneumothorax induced by video assisted thoracoscopic surgery – Surgical treatment option in the modern management of pulmonary tuberculosis – Case presentation
Olga Duniala1, Cristian Paleru1, Adrian Istrate 1, Cristina Popa2, Genoveva Cadar3, Ioan Cordos 1.

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P2688

Artificial therapeutic pneumothorax induced by video assisted thoracoscopic surgery – Surgical treatment option in the modern management of pulmonary tuberculosis – Case presentation
Olga Duniala1, Cristian Paleru1, Adrian Istrate 1, Cristina Popa2, Genoveva Cadar3, Ioan Cordos 1. 1Thoracic Surgery, National Institute of Pneumology, Bucharest, Romania; 2Pneumology, National Institute of Pneumology, Bucharest, Romania; 3Anesthesiology and Intensive Care, National Institute of Pneumology, Bucharest, Romania

Introduction: Pulmonary tuberculosis (PTB) multidrug resistant (MDR) is still a major global health problem. After the discovery of antimycobacterial therapy the use of therapeutic pneumothorax (TP) decreased. Increased prevalence of PTB
TD, multiple adverse effects and high cost of TB drugs have returned the attention to this old method of treatment.

**Objective:** The aim of this paper is to highlight the usefulness of TP induced by video assisted thoracoscopic surgery (VATS) as adjuvant therapy in cavitary PTB MDR.

**Method:** A 27-year-old, male patient was diagnosed with cavitary MDR PTB. Because the individualized treatment has proved ineffective and the patient denied resection surgery, we performed repeated intrapleural air insufflations. In the absence of satisfactory lung collapse due to pleural adhesions, it was decided to associate a minimally invasive surgical procedures – VATS. Multiple adhesions localized to the right upper lobe and 6 right segment were destroyed (monopolar cautery, LigaSure) with full release of the lung. Pleural cavity was controlled with a single tube which was maintained clamped until his removal in the first postoperative day.

**Results:** The surgical procedure was well tolerated without major complications and with sufficient parenchymal collapse, subsequently maintained by periodic air insufflations. After 4 months the patient was smear and culture negative and the cavity was reduced in size.

**Conclusions:** In carefully selected cases, TP is an effective adjuvant procedure in the treatment of MDR PTB. VATS is useful for lysis of adhesions when lung collapse is insufficient.

**P2688**

**A case of breast tuberculosis in developed country with low incidence of tuberculosis**

Veronika Polcova, Martina Vasakova, Emilia Kopecka, Jiri Homolka. Pneumological Department, 1st Medical Faculty and Thomayer Hospital, Prague 4, Czech Republic

The Czech Republic belongs to the countries with low incidence of tuberculosis We present a very rare case of breast tuberculosis (TB) resembling a breast malignancy or non-specific abscess to document the possibility of misdiagnosis and diagnostic challenge.

**Objectives:** Differential diagnosis of a painful, firm lump in a breast of 81 years old female. Review of important issues relating to the diagnosis, clinical features, and management of breast tuberculosis.

**Case presentation:** A 81 year-old female without medical history of TB was hospitalised for a painful, firm lump in her right breast. Neither the mammography nor histology confirmed the diagnosis of breast carcinoma. Chest radiograph, chest CT scans and sputum smear or cultivation did not prove lung TB. Bronchoscopical examination showed atrophic bronchial structures without bronchial granulations or fistulas. Both bronchial biopsy and bronchial aspirate were negative for Mycobacterium tuberculosis. The pathologists in the biopsy of the breast lesion described a combination of epitheloid cell granulomas and caseous necrosis. Microscopic analysis of the lump pus confirmed the presence of acid-fast bacilli. Lump pus cultivations were positive for Mycobacterium tuberculosis. A four-drug regimen (isoniazid, rifampicin, ethambutol, and pyrazinamide) and local lavage described a combination of epitheloid cell granulomas and caseous necrosis. Microscopic analysis of the lump pus confirmed the presence of acid-fast bacilli. Lump pus cultivations were positive for Mycobacterium tuberculosis. A four-drug regimen (isoniazid, rifampicin, ethambutol, and pyrazinamide) and local lavage with AT drugs led after two months to the remission of the lump and healing of the fistula.

**Conclusion:** In breast TB the clinical and radiological features are not specific. The misdiagnosis with the carcinoma of the breast or non-specific abscess is possible. Even in countries with the low incidence of tuberculosis the TB of the breast can be observed.
almost doubled from 4.9% to 8.5%, mostly due to co-morbidity with HIV. Bone and joints TB increased from 20.3% to 30.8%, and among this group especially TB spondylitis with neurological disorders, the most debilitating form of the disease. The proportion of UGTB decreased from 42.9% to 33.9% with change in gender distribution from male: female of 1:2.9 in 1999 to 1:1.8 in 2008. In contrary, there was a decrease of peripheral lymph nodes TB from 16.7% to 11.1% in 2009. TB of the thymus and the thymus still frequent. At the end of the last century out of TB in Siberia accounted for 7.4% and in 2008 (in 2009 listed in “others”) for 4.4% of the patients with EPTB. Accordingly, in 1999 other form of TB accounted for 7.8% and in 2009 4.9%.

Conclusion: In Siberia there is still a severe epidemic situation now. Low living standard, poverty, as well as poor knowledge and ignorance of EPTB both by medical service and population lead to late diagnosis of EPTB with complicated multi-organ forms.

P2692 Prostate biopsy for diagnostic of prostate tuberculosis
Denis Kholtobin, Ekaterina Kulchavenya. Urogenital, Research TB Institute, Novosibirsk, Russian Federation

World Health Organization (WHO) recognized tuberculosis (TB) as a global problem, but meant TB as a whole, mostly pulmonary TB, although 77% men died from TB, had prostate TB, mostly overlooked alive. Prostate TB has an importance due to: 1. It is a sexually transmitted disease; 2. It leads to infertility; 3. It results from sarcoidosis, but meant TB as a whole, mostly pulmonary TB, although 77% men died from TB in Siberia accounted for 34.4% had active TB of another localization, mostly – pulmonary. Results of PCR: HPV – 10.3%, Ureaplasma – 2.2%. Mycobacteria culture was positive in 6.9%. Pathomorphologically in 94.6% inflammation was found, in 65.6% – fibrosis, in 9.7% – intraprostatic neoplasia, in 5.4% - cancer, in 27.4% - TB.

Conclusion: The diagnosis of prostate TB is a very difficult task, because clinical features and laboratory signs are not-specific. Pathognomonic symptom is a cavern, but caverns mean late-diagnosed complicated form, cavernous prostate TB can’t be cured neither chemotheraphy nor by surgery. Prostate TB in early infiltrative non-cavernous stage may be diagnosed by PCR, culture or pathomorphology. Possibility of these methods alone is poor, it is necessary to use its in combination.

P2693 Masks of kidney tuberculosis
Denis Kholtobin, Ekaterina Kulchavenya. Urogenital, Research TB Institute, Novosibirsk, Russian Federation

Introduction & objectives: Urogenital tuberculosis (UGTB) is the second most common form of TB in countries with a severe epidemic situation and the third most common form in regions with low incidence of TB. 77% of men who died from tuberculosis of all localizations had prostate tuberculosis which had mostly been overlooked during their life time. In actual figures, this means about 19,000 men yearly in Russia. The main reason for late diagnosis is an atypical clinical feature of UGTB, it courses under the mask of another disease.

Material & methods: We analyzed 816 history cases of UGTB patients to estimate clinical features.

Results: Most common complains were flank pain (56.8%), dysuria (48%) and re nale colic (24%); laboratory signs - pyuria (78%) and haematuria (34%). Patients were treated by urologists or GPs with diagnoses pyelonephritis (27%), cystitis (43%), cancer (8%) or urolithiasis (22%) during 5.6 years on average. Positive smear was in 17% and positive culture of Mycobacterium tuberculosis was in 44%: 64% were diagnosed in late complicated cavernous stage, when surgery is necessary – and 96% of operations were nephrectomy due to total involvement of kidney tissue.

Conclusions: Most common masks of UGTB are pyelonephritis, cystitis and urolithiasis. UGTB presents non-specific symptoms and laboratory findings, ex-cept for positive MIB culture, but only about 44% cases are culture-positive. This is one of the main reasons for late and poor diagnosis of UGTB. The significance of UGTB may be considerable when the high prevalence of overall TB and the asymptomatic nature of UGTB are taken into account.

P2694 The reasons for late diagnosis of nephrotuberculosis
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Introduction: In fact nephrotuberculosis (NTB), like any other infectious disease, potentially can be cured by chemotherapy. But this statement is valid only for early diagnosis; actually more than 60% new-revealed patients are diagnosed late, in cavernous stage, when surgery is indicated. The aim of study was to identify the reasons for late diagnosis of NTB.

Material and methods: 167 patients with nephrotuberculosis were enrolled in study. History cases were detailed analyzed to determine clinical features, previous therapy and a level of kidney destruction in time of diagnosis tuberculosis.

Results: 11 (6.6%) had acute onset like pyonephrosis, and were operated without previous therapy. Diagnosis was verified after surgery. Other 156 had chronic NTB with clinical features specific for chronic pyelonephritis and cystitis. 59 (37.8%) were revealed in small-destructive stage of nephrotuberculosis - papillitis. 47 patients among them (79.7%) were treated with optimal antimicrobials, that means drugs don’t influence on Mycobacterium tuberculosis (nitrofurantoin, gentamycin, amoxycillin, cephaloridin). Average time of correct diagnosis in this group was 4.7 months. 97 patients in cohort (62.2%) had cavernous NTB. The main reason was prescription to 75.3% amycacin, rifampicin and fluquinolones that disguised, changed clinical features of NTB and resulted in long time of diagnostic – on average 27.4 months.

Conclusion: Nephrotuberculosis often mimics at chronic pyelonephritis and cystitis. Using amycacin, rifampicin and fluquinolones for therapy these diseases before excluding of NTB resulted in late diagnoses cavernous forms of NTB. Probably this statement is actual for region with severe epidemic situation, like Siberia.
P2697
Mycobacterial characteristics of tuberculous lymphadenitis in a tertiary care hospital in India
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Introduction: Tuberculous lymphadenitis (TBLN) shows geographical variations. In developing countries, Mycobacterium tuberculosis is common pathogen, while in developed countries nontuberculous mycobacteria are common pathogens. Bacteriological studies are necessary to confirm the diagnosis and for proper management.

Aims: To study: 1. Mycobacterial smear and culture positivity rate in histologically proven tuberculous lymph nodes. 2. Cultural characteristics of mycobacteria. 3. Prevalence of multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis.

Methods: Lymph node smear for acid-fast bacilli (AFB) was done by Ziehl-Neelsen method, and culture was done by radiometric method (MB/Bact 240 system). Sensitivity tests for antitubercular drugs were performed by conventional method on LJ medium.

Results: During Jan. 2005 to Sept. 2010, mycobacteria were grown on 74 cultures. 72 cultures (97.3%) were positive for Mycobacterium tuberculosis, and only 2 (2.7%) were positive for M. Kansui. In 89 histopathologically proven positive cultures of TBLN, 56 (62.9%) cultures were positive and AFB smear positive in 21 (23.6%) patients. In 18 culture positive patients, histopathology of lymph nodes was not available. MDR TB was present in 12 (16.2%) cultures. XDR TB was not detected.

Conclusions: 1. Mycobacterium tuberculosis is the common organism in TBLN. 2. In histopathologically proven patients with TBLN, mycobacterial smear and culture positivity rates were 23.6% and 62.9% respectively. 3. MDR TB was present in 16.2% of patients.

References:

P2698
A prospective observational study to determine the adequacy of 6 months antitubercular therapy in tuberculosis mediastinal lymphadenopathy
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Background: The present study was designed to evaluate adequacy of 6 months antitubercular therapy (ATT), Revised National Tuberculosis Control Programme (RNTCP) Cat I with isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) followed by HR thrice weekly in patients with tuberculosis mediastinal lymphadenopathy (TML).

Material & methods: 75 cases of significant mediastinal lymphadenopathy on computed tomography enhanced chest CT (CCT Chest) and diagnosis of Tuberculosis on transcortical needle aspiration were included. All patients were given 6 months ATT [2HRZE (6H)] per RNTCP and followed up after the end of 2.5 and 6 months for clinic-radiological assessment. CCT Chest done at the end of 6 months and treatment was extended with HR, in patients with persistent significant lymphadenopathy (>1 cm on CT chest). Repeat CCT chest was done 3 monthly till complete radiological response.

Results: Mean age of patient was 27.5±14.38 years with M:F ratio of 3:2. Common symptoms were fever (88%), dry cough (70%) and anorexia (60%). Right paratracheal (73%), Pretracheal (67%) were commonest lymph node groups involved. Only 15 out of 75 patients (20%) showed evidence of complete clinicoradiological improvement at end of 6 months while 5 (6.67%) patients were lost to follow up. Remaining 55 patients needed extended treatment (HR), 46 (61.33%) patients had complete clinicoradiological improvement at end of 9 months, while 9 (12.2%) patients required 12 months ATT.

Conclusion: 74% of the patients with TML required ATT for more than 6 months (<9-12 months) compared to 20% of the patients in whom 6 months ATT was adequate. The results suggest that 6 months RNTCP Cat I is inadequate for treating TML.

P2699
Comparison of treatment of TB lymphadenitis with daily or intermittent chemotherapy
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Relatively better cure rates are noted with use of daily TB chemotherapy regimens compared to intermittent regimens for TB lymphadenitis in our clinical experience. We therefore did a randomized comparative prospective study of daily vs. intermittent chemotherapy for cases with TB lymphadenitis. A total of 170 cases were randomly put on daily or intermittent regimen. Any cases of proven or suspected drug resistance were excluded. The regimens were selected as per the standard DOTS categories. 81 on daily and 73 on intermittent regimens completed their treatment and were available for analysis. 73/81 (90.12%) on daily regimen and 52/73 (71.23%) on intermittent regimens were cured. 170/170 (100%) and 23/23 (100%) respectively completed their treatment. 26/81 (32.09%) and 18/73 (24.65%) had adverse effects of chemotherapy on daily vs. intermittent treatment respectively. Daily TB chemotherapy seems to be superior to intermittent chemotherapy in terms of treatment outcome at the cost of slightly more adverse effects, in our study of TB lymphadenitis.

P2700
Demographic, clinical, and radiographic assessment of symptomatic, smear-negative pulmonary tuberculosis in a public-private mixed DOTS setting in Iloilo City
Raymond Lee 1, Malbar Ferrer 1, Lorelei Sinnit 1, Rodruse Guzman-Triviales 3, Rosario Cabana 1, Anne Lourdes Ponje 1, Elia Mae Drivmagracia 1, Elcie Solito 1
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Background: Annually, numerous cases of pulmonary tuberculosis are being referred to Public-Private Mixed DOTS (PPMD), and in most instances, they are of sputum smear-negative type. Clinicians need to decide when to initiate empiric anti-Koch’s treatment based only on symptoms and radiographic findings, as a delay in the commencement of treatment could cause further transmission of the disease. Thus, an advocacy, heralded by a TB diagnostic committee, of treating smear-negative patients suspected of having active TB disease was started.

Study objective: To recognize the clinical, radiographic, and demographic profiles of all sputum smear-negative patients with symptomatic PTB enrolled in the Directly Observed Treatment Short-Course program of St. Paul Hospital-Iloilo (DOTS-SPH) from January 2008 to June 2009.

Design: Retrospective descriptive study
Setting: PPMD (DOTS-SPH) in Iloilo City

Patients: Total of 74, symptomatic smear-negative TB patients enrolled in DOTS-SPH was included in the study.

Results: About half (51.4%) of the patients included in the study were females, mostly young adults (31.1%) in their productive years, residing in the urban areas (73.0%). Patients presented with cough (85.1%), backpain (64.9%), weight loss of >10% (44.6%), easy fatigability (44.6%), and chest pain (43.2%). The most common radiographic finding is the presence of an apical/upper lobe infiltrates (79.7%).

Conclusion: Most patients presented with at least 3 or more constitutional symptoms, cough being the most common. The initiation of anti-Koch’s medications relies mostly on chest radiographic findings and symptomatology of patients.

P2701
Post tuberculosis sequel as a important non-smoking risk factor for developing COPD
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Background: Tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) are major public health problems in developing and under developed countries. Some studies have shown a association between these two diseases (which are posing important problem for public health provider organizations).

Aim of the study: To evaluate the risk of developing COPD by previous pulmonary tuberculosis, independent of smoking.

Methods: Study includes 141 patients of COPD which were confirmed by spirometry (FEV1/FVC <0.7), were subjected to thorough history taking, clinical and radiological examination.

Results: Mean age of patients was 58.2 years. Out of 141 patients of COPD, 39 patients had a clinical and radiological evidence of previous pulmonary tuberculosis (SD 0.452, 39/141). 75 patients were having history of smoking (75/141, SD=0.504). 30 patients were identified as a non-smoker patients with previous pulmonary tuberculosis (30/141, 21.3%). In rest of the patients his mass fuel, asthama and other occupational factors were identified as a risk factor for COPD.

Conclusion: Post Tuberculosis is a one of the important non-smoking risk factor for the development of COPD.

P2702
Obstructive lung disease in patients with treated pulmonary tuberculosis
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Little is known of functional sequelae of tuberculosis. The aim of the study was to evaluate the association between chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis.

Methods: In consecutive 224 patients treated for pulmonary tuberculosis (between the ages of 20 and 82 years) who were observed at a local dispensary pulmonary function tests were performed.
Results: Pulmonary impairment was present in 105 (46.9%) patients including 81 (36.2%) patients with airflow obstruction (FEV1/FVC <0.7) and 24 (10.7%) patients with restrictive pattern (FEV1/FVC ≥0.7 and FVC or FEV1<80% predicted). Of 224 patients, GOLD criteria classified 10.3% of subjects as having mild COPD, 19.2% subjects as having moderate COPD, and 6.7% as having severe COPD. The prevalence of stage II or higher COPD in patients aged 40 and older and in younger patients was 31% and 5%, respectively (p<0.001). In patients with culture-positive pulmonary tuberculosis in the past the prevalence of stage II or higher COPD was 32% and in patients with culture-negative pulmonary tuberculosis prevalence of stage II or higher COPD was 17% (p=0.05). In patients who had two or more episodes of tuberculosis the prevalence of stage II or higher COPD was 47% and in patients with one episode the prevalence of stage II or higher COPD was 23% (p=0.01). We did not find influence of gender, smoking on the prevalence of stage II or higher COPD.

Conclusions: A microbiological cure is not the end of illness. Tuberculosis is associated with frequent airflow obstruction. Culture-positive pulmonary tuberculosis in the past and episodes of tuberculosis may increase the prevalence of stage II or higher COPD.

P2703 Airflow limitation due to COPD despite tuberculosis sequelae

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Pulmonary (P) tuberculosis (TB) and COPD are both a significant worldwide burden in terms of morbidity and mortality. They can both induce similar respiratory symptoms and airflow limitation (AFL) in smokers. To clarify if COPD can be considered in patients with TB sequelae, we retrospectively analyzed cases of patients with AFL (FEV1/FVC<0.7) and previous medical history of PTB, hospitalized between 2000 and 2010 in which diagnosis of COPD was more probable than TB sequelae because of important tobacco use and clinical history. All patients underwent CT scan to precise P lesions. Patients with PTB after COPD diagnosis were excluded and those with extended TB sequelae as well. Fifteen patients were included. Mean age was 60 years (44-83 years). Mean smoking level was 58 pack year. The mean delay between TB history and diagnosis of COPD was 20 years. Dyspnea was present in all cases and associated to chronic cough and sputum in 87% of cases. CT scan showed besides TB sequelae, P emphysema in all cases (centrolobular in 75%). AFL was severe in 80% of cases (GOLD III and IV). Treatment was based on theophylline and/or inhaled long-acting B2 agonists in all cases. All patients had clinical improvement with bronchodilator. Outcome was marked by at least one exacerbation for 13 patients due to P embolism in 2 cases, pneumothorax in 1 case and respiratory infections in all other cases.

COPD should be considered in smokers with AFL even if they have a previous history of PTB. Despite few cases of paraseptal emphysema, the majority of these patients show predominant P centrilobular and panlobular emphysema with an outcome similar to those with COPD and no PTB history.

P2704 Structure of extrapulmonary tuberculosis forms in Romania among 2007–2009

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Tuberculosis represents a major matter of public health in Romania and as a result the antituberculosis activities provided by NTP take into account also to point out all the aspects and tendencies of TB endemic.

Objective: In the context of an increased TB endemic (notification rate 99.9% 000 meaning 21457 cases in 2009) but with a decrease tendency in the last 7 years, we intended to determine extrapulmonary TB weight and structure by locations among 2007 – 2009.

Material and method: We have used information in the national data basis within the service of NTP epidemiologic supervision.

Results: Among 2007 – 2009, extrapulmonary TB weight from all sites was chronologically the following: 13,49% ±3351 cases (2007), 13,41% ±3310 (2008) and 14,51% ±3378 (2009). TB pleuresies represented 62.1% (2007), 62.1% (2008) and 58.1% (2009) of the extrapulmonary sites. In absolute figures, the other extrapulmonary sites keep a constant weight only 2 TB tibroid cases and no surrenal case.

Conclusions: Extrapulmonary TB forms among 2007-2009 keep a constant weight level within the structure of TB sites. The high level of pleuresies (with phisiognomic risk) and also the high frequency of TB meningites (severe prognosis, element of epidemiologic gravity) involve an increased responsibility in TB control.
CXR may not have sputum sampling performed, leading to underestimation of pulmonary disease.

Objectives: To determine the use of CXR & TBC in patients with EPTB & their diagnostic utility to detect co-existent PTB.

Study design: Retrospective clinical and demographic data for TB patients at our hospital (1.1.06 - 31.12.08) obtained from the London TB Register were linked to hospital microbiology & HIV test data. Baseline CXR (B-CXR) were scored by 2 respiratory radiologists blind to patient diagnosis.

Results: Of 308 cases (median age 39y, 52.9% female), 155 were notified as EPTB only, 143 (92.3%) had B-CXR, with abnormal (abN) features identified in 67 patients (46.9%): 48 (33.6%) consistent with possible PTB & 9 (6.3%) probable PTB, independent of HIV status. Sputum samples were obtained from 54 patients (37.8%). This was less likely in those with a normal B-CXR (21.4% vs. 56.2% abN, p<0.001). TBC was MTB positive in 9 patients (16.7%) suggesting with abN B-CXR (5 possible PTB, 2 probable PTB) & 2 with normal B-CXR.

Conclusion: Most EPTB patients had a B-CXR, 40% of which were consistent with possible/probable active PTB. Sputum samples were infrequently obtained, though when performed MTB yield was high. Clinical diagnosis of EPTB using B-CXR review alone may underestimate co-existing PTB. To identify infectious cases & improve TB control, sputum collection & TBC should be performed in all patients.

P2708
Assessment of the prevalence of pulmonary involvement in cases with extrapulmonary tuberculosis
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Introduction: Tuberculosis (TB) remains a public health concern worldwide. Previous reports have shown that patients with smear-negative pulmonary TB could transmit TB to others. Whereas it is a common practice to obtain a chest X-ray (CXR) for all patients with extrapulmonary TB (EPTB), sputum examinations are typically limited to those with abnormal radiographic findings suggestive of pulmonary TB.

Objective: To assess the prevalence of pulmonary involvement in patients with EPTB.

Methods: The present study included 120 patients proved to have EPTB. Patients were subjected to symptoms review, full clinical examination, chest X-ray, and sputum examination for acid fast bacilli (AFB) by direct smear and culture.

Results: The mean age of the patients included in the study was 34.4±2.13 years with gender distribution of 40% males to 60% females. All patients had histopathological confirmation of having tuberculosis while culture for mycobacterium TB was positive in 41.7% (50 patients) and direct smear examination for acid fast bacilli was positive in only 1.7% (2 patients). Normal CXR was detected in 31 patients (25.8%) regardless of the original disease, while sputum culture for mycobacterium TB was positive in 35 patients (29.2%). Although there was no statistical difference between CXR and sputum culture, the crude number was higher in sputum culture. Direct sputum examination was positive in only 6 patients (5%).

Conclusion: The prevalence of pulmonary affection in EPTB is significant. The sputum culture for mycobacterium TB is crucial to reach the diagnosis especially in patients with normal CXR or negative direct smear.

283. Clinical challenges in tuberculosis

P2709
Late-breaking abstract: Atypical chest X-ray manifestations in pulmonary tuberculosis – A case series
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Background: Majority of patients with pulmonary tuberculosis show radiological abnormalities. Atypical manifestations in the chest X-ray can occur in some patients with pulmonary tuberculosis. Knowledge and awareness about the atypical radiological manifestations will help in early diagnosis of these cases.

Aims and objectives: To find the atypical radiological manifestations in patients with pulmonary tuberculosis.

Material and methods: We compiled our data for 5 years from January 2005 to December 2010 of patients with proven pulmonary Tuberculosis with atypical chest X-ray. Patients without definitive diagnosis of Tuberculosis were excluded from the study. Diagnosis of pulmonary Tuberculosis was made when sputum AFB smear examination, Sputum AFB culture, Bronchosopic washings for AFB showed the tubercle bacilli or when Bronchosopic biopsy showed histopathology typical of tuberculosis.

Results: Atypical radiological manifestations in our study showed cavities in mid zone, lower zone, lower lung field tuberculosis, endobronchial tuberculosis, tubercular broncho pneumonia, sub pulmonic effusion and normal chest X-ray. In all these cases, clinical suspicion of tuberculosis was low as symptoms and chest the X-Ray was not typical of TB. Only one patient was HIV seropositive. Other patients did not have any immunosupression or Diabetes.

Conclusions: • All patients with any type of radiological abnormality should undergo a sputum AFB smear examination.
• All patients with chronic cough should get sputum AFB smear done even if chest X-Ray is normal
• Pulmonary TB should be considered as a differential diagnosis in any patient with chronic respiratory symptoms.

P2710
Late-breaking abstract: Tumor marker pattern in benign pleural effusion investigation. A case report of increased pleural CA 125
Marios Kougiou, George Boulbasakos, Evangelos Balti, Vassiliki Lazarou, George Tatis. Pulmonary Medicine Dept, Evangelismos Hospital, Athens, Greece

Introduction: The pleural effusion is a common occurrence in pulmonology. Measurement of tumor markers has an evolving role in diagnosis of a pleural effusion.

Methods and results: We report a case of M tuberculosis pleurisy with increased level of cancer antigen (CA) 125 in pleural fluid. The patient was a 31-year-old female, presenting with right pleural effusion. Analysis revealed a lymphatic exudate with absence of malignant cells. Microbiological examinations, staining and culture of the effusion were negative except for the mycobacterial culture. Adenose Deaminase levels were measured at 87.20 U/L. A purified protein derivative skin test was positive (16mm). Complete examination for malignancy with CT for chest and abdomen, intravaginal ultrasound and Pap smear was negative for malignancy.

Several tumor markers were measured both in serum and pleural fluid, including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA 19-9, CA 125 and Neuron Specific Enolase (NSE).

Analysis revealed a great increase of CA 125 both in serum and pleural fluid (CA 125 serum 126.9 U/ml (reference value <35 U/ml vs CA 125 pleural fluid 357.6 U/ml). The increase between serum and pleural fluid values was 182%. NSE was also increased between serum and pleural fluid by 48% (serum 8,72 ng/ml vs pleural fluid 12.91 ng/ml). AFP showed a decrease by 15%. CA19-9 also showed a decrease by 25%. CEA was measured under <0.50 ng/ml.

Conclusion: We report a tuberculosis pleurisy case with a remarkable increase of CA 125 both in serum and pleural fluid. In conclusion CA 125 could be an indicative marker for the diagnosis of tuberculosis pleurisy.

P2711
Late-breaking abstract: Cough aerosol: Significant basis to design innovative control strategies in tuberculosis transmission in smokers
Jose Gustavo Zayas1, Ming Chiao Chiang1, Eric Wong1, Fred MacDonald2, Malcolm King1. 1Medicine, University of Alberta, Edmonton, AB, Canada; 2Medicine, Caritas Research Centre, Misericordia Hospital, Edmonton, AB, Canada

Introduction: Smoking progressively alters the properties of airway mucus. Alteration in mucus responds differently to airflow interaction when coughing and may modify bioaerosol production.

Objective: Characterize the cough bioaerosol in smokers to understand its relation to the transmission of tuberculosis (TB).

Method: Cough aerosol was assessed in seven long-term smokers and compared with the aerosol of 44 nonsmokers. Measurement of the size and number of cough droplets was accomplished using a laser diffraction system.

Results: Long-term smokers emitted up to two orders of magnitude more droplets of all sizes than nonsmokers when coughing.

Average sum of cough droplets emitted by nonsmokers and long-term smokers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Droplets size</th>
<th>Non-Smokers</th>
<th>Smokers 1</th>
<th>Smokers 2</th>
<th>Smokers 3</th>
<th>Smokers 4</th>
<th>Smokers 5</th>
<th>Smokers 6</th>
<th>Smokers 7</th>
</tr>
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<tbody>
<tr>
<td>N&lt;0.5 μm</td>
<td>0.5&lt;μ&lt;1 μm</td>
<td>1&lt;μ&lt;2.5 μm</td>
<td>2.5&lt;μ&lt;10 μm</td>
<td>10&lt;μ&lt;100 μm</td>
<td>μ&gt;100 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-Smokers</td>
<td>(44)</td>
<td>1.33E+07</td>
<td>2.98E+07</td>
<td>2.78E+04</td>
<td>3.21E+04</td>
<td>1.76E+03</td>
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<td>0</td>
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<tr>
<td>Smoker 1</td>
<td>2.15E+09</td>
<td>5.03E+09</td>
<td>9.93E+08</td>
<td>1.72E+05</td>
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<td>1.91E+07</td>
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<td>1.49E+07</td>
<td>2.24E+05</td>
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<td>1.40E+08</td>
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<tr>
<td>Smoker 5</td>
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<td>1.48E+05</td>
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<tr>
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<td>3.72E+05</td>
<td>1.64E+04</td>
<td>0</td>
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</tr>
</tbody>
</table>

Conclusion: The number of droplets emitted by smokers when coughing could help to better understand the etiological association between smoking and TB. Optimal control of bioaerosol in smokers with TB, especially those with multiple and extreme drug resistance TB, might strengthen existing core TB control strategy. Acquired knowledge would lead to the development of informed public health policies, more effective practices and/or products to optimize TB control.
A 30y old male presented to A&E with sudden onset of right sided pleuritic chest pain and acutely SOB. 

Background: Previously fit and well, Asian, born in UK, no medical problems. Smoker 10-15 cigarettes, occasional use of alcohol, lives alone and work in a printing factory. No recent contact with ill person and no family history of lung diseases. 

He has been complaining of dry cough for last two months since he returned from holidays in Spain, but did not seek any medical advice. Denies any b/o weight loss, hemoptysis, fever or rigors. 

This time presented with sudden onset of sharp right sided pleuritic pain and could not breath, so brought to A&E. 

Examination/Investigations: On arrivals sats were 90% on 15l O2, tachypnic, RR30/min, clearly in respiratory distress and absent air entry on right lung, and enlarged right supraclavicular lymph node. 

Emergency chest X-ray was arranged which showed large (75%) R sided pneumothorax. An emergency chest drain was inserted after failed aspiration and repeat CXR showed good expansions of the right lung and patient was referred to the medical team. 

When seen by medical team his CXR showed reticulonodular changes on both lung fields, on top of the Pneumothorax, which was latter reported as pattern of miliary TB. 

A sputum sample was sent for AFB, had a CT head and lumber puncture done. There was no meningeal involvement. His HIV test came back as negative and was started on anti TB treatment and so far has been doing well and making good recovery. 

Learning point: Learning point was that military TB can present with pneumothorax.An emergency chest drain was inserted after failed aspiration and repeat CXR showed good expansions of the right lung and patient was referred to the medical team. 

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Although several studies have investigated the levels of C-reactive protein (CRP) in various diseases states, few have focused on its role in pleural effusion. 

The aim of this study was to evaluate the value of pleural fluid and pleural/serum CRP in segregation between tuberculous and malignant pleural effusions. 

CRP was measured in both pleural fluid and serum among 2 groups of patients, the first included 15 with tuberculous effusion diagnosed by Abram’s needle biopsy, while, the second incorporated 15 with malignant effusion diagnosed by either thorascopic or Abram’s biopsy. 

A highly significant difference was demonstrated between pleural fluid CRP in tuberculosis (29.07±4.32) and malignant (19.30±4.35) effusions. Moreover, serum CRP was significantly higher in tuberculous effusions (52.24±8.55) compared to malignant one (30.65±5.08). Furthermore, CRP pleural/serum ratio was significantly higher in malignant effusion. 

In conclusion, CRP is a useful and cheap marker for differentiation between tuberculous and malignant pleural effusion. 

The first case of mycobacterium shimoidei infection in the UK 

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Case report: We present the first case of Mycobacterium shimoidei infection in the UK. The patient is 68 years old heavy smoker with known emphysema. He was first treated for pulmonary TB in 1967 and had further 6 months of empirical therapy in 2007 for night-sweats, productive cough and new cavitating lesion. 

All cultures were negative at that time. He re-presented in 2009 with weight loss, night sweats, productive cough and arthralgia. His chest X-ray and CT scan showed new left upper-lobe cavitating consolidation. He was not immunocompromised and sputum specimens were smear negative. However all sputum cultures and a bronchial lavage were positive for Mycobacterium shimoidei, confirmed using a PCR reverse hybridisation technique. He was treated with ciprofloxacin, ethambutol, clarithromycin, streptomycin and rifabutin based on in-vitro sensitivities and previous case reports. After 12 months of treatment he is now well with negative sputum cultures. The CT scan changes have also resolved. 

Discussion: Mycobacterium shimoidei was first isolated by H Shimoide in 1975 and was described and named by M Tsukamura. Only a few cases have been reported so far. 

In conclusion, despite prevention programs, tuberculosis still remains a major international health problem. Prognosis appears to be closely related to therapeutic precocity, thus specific chemotherapy started sometimes without diagnostic confirmation.
Aims and objectives: This study aims to determine the incidence of the main adverse reactions to anti-tuberculosis chemotheraphy among patients diagnosed with active tuberculosis. HIV negatives, in S-W Romania.

Methods: The descriptive, cross-sectional, retrospective study was performed by investigating the observation sheets of all 1,138 cases hospitalized with this diagnosis in the Clinical Hospital of Infectious Diseases and Pneumophthisiology, Timisoara, between 01.01.2008-31.12.2010. The statistical processing was performed using the EPI-INFO vers. 6.04, the dichotomous variables being analysed using the b2 test and the Fisher correction.

Results: A total of 58 patients (5.02%) were identified as suspected of having pulmonary tuberculosis (TB). In 81.03% of cases (47 pts) the disease was confirmed by positive culture, CT, X-ray and histological evidence. In 18.97% of cases (11 pts) the disease was not confirmed by culture. In both cases active or latent TB was rejected after screening, PT treatment was not administrated and TB look like primary infection. Another problem was to monitor latent TB, when positive TST (in 51 pts) can not be strong argument for re-PT. Positive IGRA were obtained in 12 of these pts (23.5%) and reduced the number of PF quarter.

Conclusion: In countries with high and medium prevalence of TB not only screening before TNF-ant administration is essential. It is necessary to follow up all pts with regular (every 6 months) IGRA, which only can show the initial exacerbation of latent TB infection or new exogenous infection.

P2720 Outcome results of anti-tuberculosis treatment in latent or manifest tuberculosis patients featuring granulomatosus uveitis

Serge Borisov1, Irina Solov’eva2, Lidia Guntupova1, Lydmila Slogotskaya1, Elena Khachatarians1,2,3

Abstract P2720

Background: The tumor necrosis factor antagonists (TNF-ant) are high effective agents, but their essential effect is to increase the risk of tuberculosis (TB) development. In this paper we aimed to determine the incidence of anti-tuberculosis chemotherapy among the patients taking TNF-ant.

Methods: During the eight years of study, 178 HSCT patients have been admitted in our institution for infections is limited.

Records from all allogeneic HSCT patients admitted in our institution for mycobacterial infection from January1, 2003 to December 31, 2010 were reviewed.

Results: During the eight years of study, 178 HSCT patients have been admitted

MONDAY, SEPTEMBER 26TH 2011

P2718 Pulmonary diseases due to non-tuberculous mycobacteria in TB referral

P2719 Screening and monitoring of tuberculosis in patients on tumor necrosis factor antagonist therapy

Legend: ND, not determined; *Deceased unrelated to mycobacterial infection; NED, no evidence of disease; ALL, Acute lymphoid leukemia; AML, Acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; ADCL, acute dendritic cell leukemia; R, rifampicin; H, isoniazid; E, ethambutol; Z, pyrazinamide; C, clarithromycin; M, moxifloxacin

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for pulmonary complications. 7 patients have had a diagnosis of mycobacterial infection.

Conclusions: Mycobacterial infection is rare (4%) in French HECT patients with pulmonary complication. The infection is lung limited. It usually occurs in the first post-transplantation year. The clinical course under treatment is favorable in most cases.

P2722

Spinal tuberculosis in South London Hospital – A 5 year review of our experience

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Introduction: The incidence of tuberculosis (TB) in southeast London has risen by 25% over the last 10 years and is 4 times greater than the national average. Extra pulmonary involvement is seen in 47% and spinal TB accounts for 2-3% of cases. Diagnosis of spinal TB can be delayed due to nonspecific nature of symptoms.

Aim: To determine our experience of managing spinal TB at Queen Elizabeth Hospital in Woolwich, UK.

Methods: A retrospective case note review of recorded data was performed of all the spinal TB patients referred to QEHS over 5 years (Jan 2006- 2011). 27 out of 34 patients had case notes available for review. Mean age at diagnosis was 47 years (range 20-78 years). 88% of patients presented with back pain, with or without neurological compromise.

The overall incidence of spinal TB was 5.6% (national average 2.3%). The mean delay was 81 days (3-430) from onset of symptoms to first presentation and 99 days (3-552) from onset of symptoms to referral. There was an average delay of 33 days (12-303) from initiation of referral to diagnosis. 47% had confirmed histological diagnosis with culture.15% had paravertebral abscesses with or without involvement seen on imaging.

Combination chemotherapy was the main modality of treatment. 24 (88%) patients were managed with combination chemotherapy alone.

Further details into the delays and consequences were looked into.

Conclusion: This study highlights that awareness of demographic and local incidence, together with high index of clinical suspicion in areas with relatively high incidence would facilitate early diagnosis and treatment of spinal TB.

P2723

Immunological status of TB/HIV dual infection patients in Latvia in year 2009

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1Department of Infectology and Dermatology, Riga Stradi University, Riga, Latvia; 2Clinic of Tuberculosis and Lung Diseases, LIC, Riga, Latvia

In the world tuberculosis (TB) is main cause of illness and death for human immunodeficiency virus (HIV) patients. Situation among TB/HIV dual infection patients in Latvia is relatively unexplored.

Aims: To analyse incidence of various TB clinical forms among HIV patients incidence of resistant TB among TB/HIV patients and medium immunological parameters for TB/HIV patients at the moment of TB diagnosis anti-TB therapy and HIV infection results for TB/HIV patients.

Materials and methods: In retrospective study case histories for 61 from 73 patients diagnosed in year 2009 with TB/HIV dual infection were analysed.

Results: For 72% (43) patients HIV was diagnosed before TB diagnosis, 28% (17) patients HIV and TB were diagnosed simultaneously. In 80% (49) TB was diagnosed for first time, in 20% (12) relapse. In 40% (25) multiorgan TB infection was diagnosed, in 30% (18) infiltrative pulmonary TB, in 25% (15) disseminated pulmonary TB and in 5% (3) extra pulmonary TB. In 60% (37) cases TB was sensitive to all antiTB drugs, in 35% (21) resistant cases. Medium CD4+ cell count was 294 cells/mm3 (min–6, max–2003). 67% (41) patients received full,18% (11) disrupted therapy and 13% (9) cases were lethal.

Conclusion: In year 2009 significant number of TB and HIV were diagnosed simultaneously. Pulmonary TB dominates among TB/HIV patients, but there is also high number of patients with TB multi-organ infection. There is high number of resistant TB among HIV/TB infected individuals. High CD4+ cell count could indicate high incidence of TB among HIV/TB individuals. There is significant number of cases where TB is cause of death in TB/HIV dual infection patients.

P2724

New biomarkers for LTBI in IGRAs supernatants

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Background: Commercial in vitro T-cell interferon gamma (IFN-γ) release assays (IGRAs) including the QuantiFERON® tests have been introduced into clinical practice for the diagnosis of Mycobacterium tuberculosis. However, the sensitivity of the IGRA may not be as high as expected in patients with immunodeficiency patients.

Aim and objectives: To assess whether alternative biomarkers could be used in future developments for diagnosis of TB.

Methods: We recruited twenty-four latent TB patients and 46 healthy controls at National Center for Geriatrics and Gerontology in Japan and performed the OFT test. To investigate the ability of new host markers to differentiate between LTBI and controls, levels of IL-10 and IFN-γ as Th1 cytokines, TARC and MDC as Th2 chemokines, and IL-8 as a neutrophil chemotactic factor in QFT supernatants were evaluated using an enzyme-linked immunosorbent assay.

Results: Levels of IP-10, TARC and MDC were significantly increased in LTBI patients compared with controls. Levels of TARC and IL-8 were not different between two groups. The levels of IP-10, TARC and MDC were not correlated with levels of IFN-γ.

Conclusion: IP-10, TARC and MDC had diagnostic potential as they could differentiate between the LTBI patients and the controls. IP-10 seemed most promising as they were expressed in high levels in the LTBI patients and were low in the control samples. Further studies are needed to explore the potential of these highly expressed novel biomarkers individually and in combination.

P2725

Mouse model of pulmonary disease after aerosol infection with mycobacterium xenopi

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Rationale: Opportunistic respiratory infections due to M. xenopi are on the rise in industrialized countries and current therapies are inadequate. Only two examples of Mycobacterium xenopi, a streptomycin-resistant strain and the beige Swiss mouse models re-infected have been performed so far. As aerosol inhalation is the probable route of infection in humans, we hypothesized that aerosol infection of mice would better recapitulate human infection and permit better assessment of the response to antibiotic treatment. Our primary objective was to determine which strain of mice was the most susceptible to aerosol infection.

Methods: Four strains of mice were tested: BALB/c, C57Bl/6, Beige, and athymic nude (Nude). For each strain, thirty 6-week-old females were simultaneously aerosol infected with 4.7 log10 of M. xenopi ATCC # 19971. At 1, 2, 3, 4, 8, 12 and 23 weeks post-infection, three mice per group were sacrificed for gross lung lesions, spleen weight, and lung and spleen CFU counts. From week 4 to 12, 9 mice of each group were treated with clarithromycin 100 mg/kg daily 5 days a week. Three treated mice per group were sacrificed at week 8 and 12.

Results: In BALB/c, C57Bl/6, Beige and Nude mice infected with M. xenopi, the lung CFU counts steadily increased to reach 5.92, 5.99, and 5.75 log10, respectively at week 4; 6.35, 6.72, 6.60 and 6.93 log10, respectively at week 8; 6.51, 6.43, 7.69, and 6.63 log10, respectively at week 12; and 6.59, 6.72, 8.16, 7.32 log10, respectively at week 24. In all mice, M. xenopi disseminated to the spleen. Clarithromycin treatment reduced significantly, by 2 log10, the lung CFU counts in all strains of mice.

Conclusion: Nude mice were the most susceptible to aerosolized M. xenopi infection.

P2726

Patients with a lung cancer are changed: About a French monocentric cohort between 1990 and 2010


<table>
<thead>
<tr>
<th>Sex &amp; male/female</th>
<th>7.3</th>
<th>5.6</th>
<th>2.9</th>
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<td>65</td>
<td>67</td>
<td>65</td>
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<tr>
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<td>8%</td>
<td>8%</td>
<td>12%</td>
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<tr>
<td>Alcohol consumption</td>
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<td>57%</td>
<td>47%</td>
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<tr>
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<td>32%</td>
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<td>9%</td>
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<tr>
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<td>15%</td>
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</table>

284. Epidemiology of lung cancer and screening
Methods: see table.

Results: This analysis shows the increase of adenocarcinoma with increase of female patients, of non-smoker-status and increase of diagnosis by TDM function. Non small cell is stable.

Background: Individualized treatment in lung cancer (LC) needs precise characterization of the tumour and host. Data on the impact of diabetes mellitus (DM), the most frequent endocrinological disorder, on the prognosis of lung cancer is conflicting.

Aim: To define the importance of DM for survival in lung cancer.

Method: We analyzed data from a large cohort study, the Nord-Trøndelag Health Study (HUNT study) linked to the Norwegian Cancer Registry, and controlled the results using two lung cancer studies, the Pemetrexed Gemcitabine study (PEG study) and the Norwegian Lung Cancer Bio Bank (NLCB). Survival rate between lung cancer patients with and without DM were compared using the Kaplan-Meier model and Cox regression analysis.

Results: Of a total number of 107 127 study participants there were 5448 persons with DM and 1877 cases of LC. Among the LC patients 85 patients had DM. LC patients without DM showed 43%, 19%, 3% versus 28%, 11%, 4% 1-year, 2-year and 3 year survival in patients with and without diabetes showed 43%, 19%, 3% versus 28%, 11%, 4%, respectively. With the Cox regression model we adjusted survival for DM, age, gender, histological type and smoking status. The first five confounders showed to be independent factors (p < 0.001), while smoking status was not (p = 0.531).

Conclusion: Lung cancer patients with diabetes mellitus has an increased survival compared to patients without diabetes mellitus. The magnitude of the survival benefit seems to be of clinical importance and therefore justified to be studied more in detail.

P2729 COPD prevalence in lung cancer patients – Is COPD a risk factor for lung cancer?

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Background and aim: Chronic obstructive pulmonary disease (COPD) is a common comorbid disease in lung cancer, estimated to affect 40–70% of lung cancer patients. As smoking exposure is found in 85–90% of those diagnosed with either COPD or lung cancer, coexisting disease could reflect a shared smoking exposure. We aimed to investigate the prevalence of COPD in patients diagnosed with lung cancer.

Methods: We analysed 1173 patients diagnosed with lung cancer in Internal Medicine Department between 2000 and 2010 for the presence of lung cancer risk factors.

Results: A number of 1046 patients (89.17%; p < 0.0001) were former smokers/actively smoking. Preexisting disease was diagnosed in a number of 442 cases (37.68%) COPD in 257 cases, and other etiologic factors in 185 cases (58.14% versus 41.85%; p < 0.0001). Histopathologic results were available in 131 cases and showed: squamous carcinoma (n=78; 59.54%), adenocarcinoma (n=24; 18.32%), large cell undifferentiated carcinoma (n=11; 8.39%), and small cell carcinoma (n=18; 13.74%). Smokers versus non-smokers and COPD prevalence according to histopathologic types were the following: the 71 versus 7 (p=0.0001), and 14 cases of COPD (17.94%) for squamous carcinoma; 15 versus 9 (p=0.1482), and 2 cases of COPD (13.33%) for adenocarcinoma; 8 versus 3 (p=0.8961), and 1 case of COPD (9.09%) for large cell undifferentiated carcinoma; and 14 versus 4 (p=0.0022), and 3 cases of COPD (16.66%) for small cell carcinoma.

Conclusions: Our study shows a high prevalence of COPD in lung cancer patients. COPD was the second most important risk factor for lung cancer, after smoking. The most important relationship of COPD was with the squamous type lung cancer.

P2730 Peculiarities of lung cancer in patients with COPD

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The aim of the study was to determine main causes of mistakes in radiologic diagnose of lung cancer in patients with COPD. We examined 201 patients with moderate and severe COPD admitted to hospital during exacerbation. All patients were examined by MDCT angiography interpreted by two experienced radiologists, also previous CT scans were compared with the acquired data.

We founded cancer of main bronch in 15,3% of patients with severe, and in 8,6% of patients with moderate COPD. Peripheral lesions were observed in 17,9% of patients with severe and 5,5% of patients with moderate COPD with significant interobserver consensus. During analysis of earlier CT examinations (a 5 year period) in 1,9% central cancer was not determined on early stage of disease, because study was performed without contrast enhancement. Peripheral neoplasms were not determined because of peribulbous growth, looking like thickening of the wall...
of bulla in 1.4% of patients, cancer growing in the place of fibrosis - 0.4%, fluid of different genesis in bullas in 1.4% of patients. Interobserver consensus was significant in determination of lesions on previous scans. We observed a group of patients after lung volume reduction surgery who were thoughtfully examined before the treatment and who than developed different types of cancer in a short period after the surgery. No evidence of malignancy was founded on previous scans, so we can only speculate that surgery and changes in circulation were triggering mechanisms in the extraordinary quick development of tumors.

Thus we can suppose that in patients with COPD contrast enhancement is strongly recommended for early diagnosis of tumors, and patients after LVRS should be examined by CT after surgery.

P2731 Epidemiological and histologic features of lung cancer in Montenegro
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Background: Lung cancer is one of the most common malignant neoplasms as well as the most common neoplasm stated as a cause of death. Epidemiological characteristics of lung cancer differ among countries and regions.

Aim: To determine the epidemiological and histologic features of lung cancer in Montenegro.

Methods: Study group comprised patients in Montenegro in continuous period 1997-2010.

Results: In reported period number of newly diagnosed lung cancer is 2497. The incidence ranged from 29.8 in 1997 to 35.9 in 2004. Out of the total number of diagnosed lung cancer, epidermoid carcinoma was diagnosed in 1484 cases (58.6%), small cell lung carcinoma (SCLC) in 597 cases (23.92%) and adenocarcinoma in 416 cases (16.65%). The men were represented with 83.17% (2078) while the female were 16.83% (419). Ratio of smokers and nonsmokers for each histological type was (epidermoid 8:1, 2:1 adenocarcinoma, SCLC 9:1). The most frequent histopathological type in males was epidermoid (63%) followed by adenocarcinoma (14.5%) and then SCLC (22.5%). In women the most common cancer was epidermoid (43.5%). Adenocarcinoma accounts for 26.5% and SCLC with 30%. The percentage of smokers was 88.72%, nonsmokers represented 11.28%.

Conclusion: During the period 1997-2010 a significant increase in the incidence of diseases such as lung cancer was not observed, but the decrease in the frequency of epidermoid carcinoma was noted - from 75% (1997) to 50% (2010) as well as the increased frequency of SCLC from 1% (1997) to 30% (2010) and adenocarcinoma from 13% (1997) to 28% (2010).

P2732 Occupational exposure to carcinogens and lung cancer: Impact of a dedicated professional disease consultation in a Belgian oncologic centre
Anne Pascale Meert, Isabelle Morelle, Thierry Berghmans, Ingrid C.S. Toth, Jean Paul Sculet. Thoracic Oncology and Intensive Care, Institut Jules Bordet, Brussels, Belgium

Introduction: In epidemiological studies, 15% of lung cancers in men and 5% in women are linked to occupational exposure to carcinogens. However, there is a clear under-reporting of occupational lung cancer in Belgium: in 2006, only 67 cases were recognized by the Professional Disease Fund whereas 500 were attended.

Aim: To appreciate the frequency of occupational lung cancer in newly diagnosed lung cancer in a Belgian oncologic hospital.

Material and method: Since 01/09/2009, all new patients with lung cancer were sent to a dedicated consultation where a physician trained in professional diseases was asked information about job history and look for known or suspected lung carcinogenic exposure.

Results: 73 job stories have been recorded, 23 patients (32%) were certainly or probably exposed to a lung carcinogenic agent (known or suspected). All the patients were men (mean age 62 years), 22 workmen, 21 were smokers. Asbestos was the most common carcinogenic agent found (25%). Ten claims for occupational disease were made; 3 recognized and 7 are pending.

Conclusion: This study shows the utility of a physician with knowledge in occupational pathology into a clinical department to reduce the under-reporting of occupational primary lung cancer and then to ensure that the victims receive the appropriate medicolegal benefits.

P2733 The association between residential radon concentration and lung cancer
Doina Adina Todea1, Loredana Elena Rosca2, Constantin Cosma2, 1Bronchology, Hospital for Lung Disease, Brezova, Montenegro, Nikic, Montenegro, Serbia, 2Department of Anatomy, Medical Faculty, Montenegro, Podgorica, Montenegro, Serbia

Histology 68% 87%
Male:Female 1.4:1 0.84:1

Lung cancer represents the most frequent cause of mortality caused by malignant

P2734 Is female gender a protective factor for NSCLC patients? A follow up study of 20 years of 478 patients
Jose Chatkín, Norris Scaglia, Jose Figuereido-Pinto. Medicine, Pontificia Universidad Catolica do Rio Grande do Sul, Porto Alegre, Brazil

Background: Previous studies reported a better survival rate among females with non-small lung cancer (NSCLC). We have previously also registered similar findings. The purpose of this study was to re-evaluate female gender as a protective factor survival in a cohort of patients with NSCLC in a follow up study of 20 years.

Methods: In a retrospective cohort study, we examined the survival rates of 478 NSCLC patients who underwent surgical curative treatment at Hospital da PUCRS, in Porto Alegre, Brazil between January 1990 and December 2009. Survival rates were analyzed by Kaplan-Meier plots and by the log rank test. Cox proportional hazards analyses were performed to identify potential confounding factors. The statistical significance was considered as P=0.05.

Results: The 5-year survival rate was 55.6% for women and 38.8% for men (P=0.005), when considering the whole group of patients. After adjustment for possible confounding factors (age, TNM stage, histology, tumor size, surgical procedure, smoking load, hemoglobin, and postoperative complications), female gender protective effect persisted only for stage I (survival rates: 75.2% and 47.9%, for women and men, respectively; P<0.007). For subjects in stages ≥II, no significant differences in 5-years survival rates were found. The hazard ratio for males in stage I was 1.95 (95%CI: 1.16 to 3.27, P=0.012), when compared to females.

Conclusion: In this 20 years of follow up study, female gender was a protective factor for mortality in patients with NSCLC submitted to surgery with curative intent in stage I when compared to males. This effect is not observed in patients in stage ≥II.

P2735 A retrospective study of lung cancer in young patients
Pradeep Rajagopalan, Douglas George Price, Sivananam Sasikumar, Ramin Baghi Ravary, Neil Robert Goldsack, Brett Pereira. Respiratory Medicine, Kent and Canterbury Hospital, Canterbury, Kent, United Kingdom

Introduction: Over-representation of women, more advanced disease staging at presentation, better performance status and similar survival figures have been noticed in younger (<50 years) lung cancer patients as compared to the general patient population with the disease.

Objective: A retrospective study (February 2010) was done to derive clinicopathological data from young lung cancer patients treated in our hospital in the last 5 years. We also compared our findings with National Lung Cancer Audit (NLCA), 2007 in the UK. The NLCA data were considered as a reflector of the patients from all age groups.

Findings: 36 patients were identified for the study. Median age was 47 (37-50), 19 (54%) were female. 76% had WHO performance status (PS1) in patients with documented PS. 43% had family history of lung cancer. 89% were current smoker. Histology was achieved in 87%. 68% had non small cell carcinoma (NSCLC) including 40% adenocarcinoma, 24% had small cell carcinoma. 3 had carcinoid. 55% of histology proven NSCLC had stage 4 disease at presentation. 86% had some form of treatment (surgery, chemotherapy or radiotherapy). 6 (18%) had resection.

NLCAs & Local Data Comparison

Male:Female 1.4:1 0.84:1
Histology 68% 87%
Stage 4 or Presentation 9% 5%
Active Treatment Received 51% 87%
Resection in NSCLC 14% 18%
Median NSCLC survival 232 246

NLCAs & Local Data Comparison

Male:Female 1.4:1 0.84:1
Histology 68% 87%
Stage 4 or Presentation 9% 5%
Active Treatment Received 51% 87%
Resection in NSCLC 14% 18%
Median NSCLC survival 232 246
Conclusion: Majority of these patients presented with advanced stage disease as in previously reported larger cohorts. Women were a majority but they had a better survival than men. 41% had positive family history suggesting a possible genetic factor. Favourable performance status resulted in higher resection rate and active treatment compared to overall patient population. But did not lead to better survival.

P2736 KRAS mutations in non-small cell lung cancer (NSCLC) – Experiences by routine molecular testing in a German lung cancer centre
Christian Boch1, Jens Kollmeier1, Daniel Misch1, Andreas Roth2, Torsten Blum1, Wolfram Gruening1, Nicolas Schoenfeld1, Thomas Manring1, Torsten T. Bauer1. 1Department of Pneumology, Pulmonary Diseases Clinic, Heckeshorn, HELIOS Kliniken Emil von Behring, Berlin, Germany; 2Institute of Pathology, Helios Kliniken Emil von Behring, Berlin, Germany

Introduction: More than 20 years ago KRAS mutations were identified but the utility of this information remains vague. Several clinical studies indicate that KRAS mutations are associated with shorter overall survival (OS) in presellected populations. With the routine testing of KRAS mutation in all newly diagnosed NSCLC in our clinic for 14 months, we offer a new perspective.

Methods: From Nov 2009 until Dec 2010, all subsequent biopsies of newly diagnosed NSCLC (n=753) obtained by surgery, routine bronchoscopy or CT guided biopsy were tested for the ability to be analysed by LightCycler Real-time PCR accessing codons 12 and 13 for the presence of KRAS mutations. The obtained data were correlated with the centre-bound tumour registry for survival data.

Results: A total of 504 cases with NSCLC, 229 adenocarcinoma (AC), 163 squamous cell carcinoma (SCC) and 112 other NSCLC were eligible for analysis. Among those, KRAS mutation was present in 79/504 cases (15.7%, male, n=39).

The highest frequency of KRAS mutation was observed in AC 61/229 (27%). Patients with SCC (61/163, 3.7%) and other NSCLC (12/112, 11%) showed KRAS mutations less often (p < 0.001). By analysing EGFR mutations in the same population, we detected only one KRAS positive patient with a simultaneous EGFR mutation. By now we did not find a significant difference in OS expressed as mean ± (SEM) (KRAS negative 37.6±6 vs KRAS positive 40.6±20, p = 0.244).

Conclusion: The frequency of KRAS mutations in NSCLC in our unselected cohort is comparable with previous reports. They are more frequent in AC compared to other histologic subtypes. To date we could not confirm any association with OS.

P2737 Characterization of patients with non-small cell lung cancer (NSCLC) relative to its EGFR mutational status
Ana Castro, Ana Antunes, Ana Barroso, Sara Conde, Sofia Neves, Bárbara Parente, Centro Hospitalar Vila Nova de Gaia - Espinho EPE, Vila Nova de Gaia, Portugal

Introduction: EGFR (Epidermal Growth Factor Receptor) mutations occur in 10-15% of non-Asian patients with NSCLC. In 2010, our Lung Cancer Centre started performing this sequencing systematically in all patients with NSCLC, regardless of histology, smoking or sex.

Objective: To identify a group of patients that undergo EGFR sequencing in the year 2010 and assess their frequency.

Methods: Descriptive statistical analysis of patients with NSCLC who did EGFR sequencing in 2010.

Results: The sequencing was performed on 126 patients, 75% males and 25% females. Average age 65 years. 69% non or ex-smokers and 31% smokers. Histology: 59%adenocarcinoma, 23%squamous cell carcinoma (SCC). Mutations were detected in 13 patients (10.3%), one mutation in exon18, 6 in exon19, 2 in exon20, 4 in exon21 and no resistance mutations were described. The mutation rate was higher in females (53%), non-smokers (46%) and adenocarcinoma (62%). Female patients with EGFR mutation: 86%non-smokers, 85%adenocarcinoma, 15%epidermoid histology. Male with EGFR mutation: 83%ex-smokers, 67%SCC, 33%adenocarcinoma. Non-smoker mutated patients were all female, 83%adenocarcinoma, 17%SCC.

Conclusion: Our group had a mutation rate of 10.3%, predominantly female, non-smokers, adenocarcinoma histology, accordingly with literature. This work also intends to highlight the importance of sequencing EGFR gene mutation in all patients with NSCLC, whereas mutation is also frequent in males, squamous histology and smokers. These patients are given the possibility of a 1st line treatment in the with TK inhibitors, with a greater increase in survival, improved quality of life and a better chance for other courses of chemotherapy.

P2738 Analysis of EGFR-mutations in a diverse urban patient population
Amanda Tuftman1, Kai Wagner2, Andreas Jung1, Rudolf Maria Huber1.
1Department of Respiratory Medicine, Campus Eppendorf, University Hospital, Hamburg, Germany; 2University of Medicine, Ludwig Maximilians University, Munich, Germany

Background: EGFR-mutations are predictive for EGFR-TKIs in advanced NSCLC, however, not all pts are screened for these mutations. Clinical crite-
These figures were significantly lower for control samples, i.e., 2%, 6%, and 2%, respectively (all P-values < 0.001). Cumulative analysis of RASSFIA methylation, i.e., combining methylation positivity outcomes for day 1-6, and day 1-9, revealed RASSFIA methylation in 39% and 47% of cases, respectively, versus 8% and 9% of controls, respectively.

Conclusion: Our study suggests that spumum collected over multiple successive days results in a gain in sensitivity, at the expense of a small loss in specificity, for the detection of lung cancer.

P2742
Molecular test supporting early lung cancer detection project based on pilot Pomeranian lung cancer screening program
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Introduction: Lung cancer is one of the most common malignant neoplasms worldwide. Only 10% of patients can be cured, mostly due to late diagnosis and high aggressiveness of lung cancer.

Aim: Aim of the Molecular Test Supporting Early Detection of Lung Cancer Project is to perform genetic studies and serum protein studies in order to increase the efficacy of radiological examinations in early lung cancer screening and to define population of particularly high risk of lung cancer development. The project consists of five thematic areas.

Results: Pomeranian Pilot Early Detection Program has been realized from the 17th November 2008. In this project 8000 healthy subjects with high risk of developing lung cancer (age 50-75, at least 20 pack-years) were screened with low-dose CT scanning of the lungs. As a co-project blood samples were taken from those patients who gave informed consent. In the first year of project realization 6836 healthy subjects were screened. In above a half of the cases (53%) at least one pathological alteration in lung tissue was found. Among 186 patients, in whom the lesion was above 1 cm in diameter, in 56 cases lung cancer was diagnosed. Almost 60% of lung cancer cases were in stage IA.

Conclusions: Pomeranian Pilot Lung Cancer Screening Program and Molecular Test Supporting Early Lung Cancer Screening Project - Moltest 2013 are dedicated to define population of particularly high risk of lung cancer development.

P2743
Current screening programs for lung cancer – Are inclusion criteria too rigorous to identify asymptomatic patients?
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Background: Preliminary results from the controlled National Lung Cancer Screening Trial (NLST) indicates a mortality reduction of > 20% in screened patients; high risk being defined as smokers (ex/current) > 55 years old with > 30 pack-years. Recent studies suggest that female smokers develop lung cancer at a younger age and following smaller amounts of tobacco consumption than males. In industrialized countries the incidence of lung cancer is falling in males, but increasing in females. We aimed to assess if the inclusion criteria used in NLST would have identified lung cancer in a cohort of asymptomatic subjects who underwent surgical resections at our tertiary university hospital.

Material and methods: During the period 2002-10 clinical data from 1043 consecutive patients with 1204 cancerous cases with lung cancer were retrospectively registered. 626 patients (294 (47%) females, mean age 68 years, and 332 (53%) males, mean age 64 years), underwent surgery. Results: Of the 626 patients who underwent surgery, 267 (42%, 131 females, 136 males) had no clinical manifestations of lung disease at presentation, and chest x-rays had been performed for co-incidental conditions. In females, 30/131 (23%) were current or ex-smokers with > 30 pack-years. In males, the corresponding proportion was 65/136 (48%). Applying the NLST criteria, 77.7% of the females and 52% of the males would not have been admitted to the screening program.

Conclusion: Less than one forth of asymptomatic females who underwent resection for lung cancer would have been included in NLST as their total consumption of tobacco in pack-years was too low. Also, half of symptom-free resected males would have been excluded from screening.
**285. Imaging, functional evaluation and staging for lung cancer patients**

**P2746**

*Is an EGF mutation associated with lower glucose metabolism in the FDG-PET?*

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**Background/Aim:** In non-small cell lung cancer (NSCLC), new therapies that target specific oncogenic pathomechanisms like the epidermal growth factor receptor (EGFR) were developed. Positron emission tomography (PET) using fluorodeoxyglucose (FDG) is routinely implemented in the diagnosis and staging of NSCLC. In this study, we analyzed the correlation between molecular markers like EGFR and the glucose metabolism of NSCLC.

**Methods:** 80 patients with NSCLC were examined with FDG-PET/CT using standard scanning protocols; routinely the maximal standardized uptake value (SUVmax) of the tumour was determined. The demographic criteria of all patients were similar, all underwent surgical excision of the tumour. The tumour tissue was characterized histological and by molecular typing, including the EGFR status. The SUV was correlated with diverse parameters.

**Results:** The tumour histology showed in 36 patients a squamous cell carcinoma (45%), in 33 an adenocarcinoma (41%) and in 11 other tumour entities (14%), the average SUVmax were 12.1 (±4.8) (±SD), 9.0 (±4.4) and 11.9 (±4.8), respectively. In only 5 patients an activating EGFR-mutation was found, all others showed the EGFR wild-type. All but one mutation were found in patients with adenocarcinoma (12.1% of that histology); these tumors showed a very low SUVmax of 4.1 (±0.9). In contrast, one EGFR-mutated squamous cell carcinoma showed a very high SUV of 20.3.

**Conclusion:** In our patient cohort with NSCLC, all patients with adenocarcinoma and EGFR mutation showed a low glucose metabolism. This finding may suggest that these tumours have down regulated metabolism and may be anticipated by lower SUV in FDG PET scans.

This study was supported by the Oskar-Helene-Heim foundation.

**P2747**

*An analysis of EGFR expression and tumour imaging in non-small cell carcinomas of lung*

Vijayalakshmi Thanasekaraan, Prathiba Duvuru, Shalinee Rao, Safienna Mohamed, Samuel John Sundar. Chest tomography was reviewed to assess for tumour features. The correlation of EGFR expression with radiological features may reveal their possible relationship.

**Aim:** To evaluate EGFR expression in NSCLC and correlate with their radiological features.

**Material and method:** Twenty -two cases of NSCLC were histologically subclassified based on WHO classification of lung carcinomas. Immunostaining for TTF-1, p63 and EGFR were performed on paraffin embedded tissue sections and their expression evaluated. Chest tomography was reviewed to assess for tumour location, diameter, contours, margins, cavitation and lymph node enlargement.

Findings of radio-imaging and EGFR immunoreactivity were correlated.

**Results:** Fourteen and 8 cases of squamous cell carcinoma were identified. Epidermal growth factor receptor expression was noted in 86.3% of tumours. About 92.8% of adenocarcinomas and 75% of squamous cell carcinomas were EGFR positive. On radiology, mean diameter of lesion was found to be 36.4mm and 6.1mm in EGFR positive and negative tumours respectively. Fourteen EGFR positive cases were well defined and five poorly defined. Each of all the eight cases with pleural effusion and regional lymphadenopathy were EGFR positive.

**Conclusion:** Major percentage of NSCLC showed EGFR expression reinforcing its utility for targeted therapy. A positive EGFR correlation was noted with tumour size, regional lymphnode enlargement and pleural effusion which reflect biologically aggressive property of EGFR positive tumours.

**P2748**

*Integrated 18F – FDG PET dynamic contrast enhanced CT to phenotype non-small cell lung cancer*

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**Objectives:** To apply molecular and functional imaging to the pre-treatment assessment of disease using combined Dynamic Contrast enhanced CT (DCECT) and18F-Fluorodeoxyglucose (FDG) PET in lung canceroma to define the cancer phenotype.

**Methods:** Seventy four consecutive patients with potentially curable lung cancer were prospectively recruited for combined positron 18F-FDG PET/DCECT using an integrated 64 detector PET/CT. There were 10 technical failures leaving a study population of 64 patients (35 males; 29 females. Mean age 67.5). Studies were using an integrated 64-detector PET/CT. The uptake of 18F-FDGPET quantified as the Standard Uptake Value (SUVmax) assessed tumour metabolism.

**Results:** The mean tumor SUVmax, PE and SPV were 13.8, 37.6 HU and 6.5. No statistically significant relationships between tumor metabolism and vascular parameters. There were significant associations between tumor size and vascular parameters - SUVmax v size (r=0.4, p=0.001), SUVPE v size (r=0.4, p<0.001). SUVmax and SUVPE were higher in SCC than in adenocarcinoma (17.4 versus11.5; p=0.026 and 0.57 versus 0.35, p=0.021 respectively). A phenotype with low metabolism and high vascularity was significantly more common amongst adenocarcinomas (p<0.01), whilst high metabolism with high vascularity was more common amongst SCC (p=0.005).

**Conclusion:** Vascularity and metabolism are uncoupled in NSCLC. Since some lung cancer patients have inadequate tissue sampling metabolic flow data could be helpful clinically in managing lung cancer patients to targeted therapy using non-invasive 18F-FDG PET/DCECT scan.

**P2749**

*FDG PET/SUVmax is an independent prognostic indicator in patients with non-small cell lung cancer*

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**Background:** FDG-PET is a commonly used non-invasive tool for diagnosis and staging of lung cancer, the leading cause of cancer death. SUVmax has been suggested to be an independent prognostic factor in patients with operable non-small-cell lung cancer (NSCLC). However, PET-CT is not recommended in patients with advanced disease.

**Aim:** Evaluate the utility of SUVmax of the primary lesion as an independent predictor of overall survival in patients with NSCLC, including advanced disease.

**Methods:** Retrospective analysis of 47 patients (29 male, median age 69 years) with NSCLC (stage I 38%, stage II 9%, stage III 34%, stage IV 18%) who underwent FDG PET at diagnosis. Cox regression analysis was applied to examine the effect of SUVmax on survival. This was then adjusted for stage, treatment, age, sex and histology.

**Results:** There was a significant difference in survival between patients who had a low vs high SUVmax, hazard ratio 3.31 (p=0.006), such that an increase in SUVmax of the primary of 5 points conferred a hazard ratio of 1.49 (p=0.013).

**Conclusion:** The relationship was maintained when multiple factors were adjusted for, with a hazard ratio for an increase in SUVmax of the primary of 5 points of 2.8 (p=0.03).

**FDG-PET provides additional information about prognosis in NSCLC, independent of stage at presentation.** The relationship between SUVmax of the primary and survival is maintained, even in patients with advanced disease.
Is our preoperative TNM staging reliable?

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Introduction: Agreement between preoperative and surgical TNM staging is usually <50%.

Aim: To compare our preoperative staging (cTNM) with surgical-pathological staging (pTNM).

Methods: Cross-sectional study of patients with lung cancer surgically treated from 1-1-08 to 31-12-09, excluding relapses or neoadjuvant therapies. Preoperative stag-

ing based on: CT scan, positron emission tomography (PET-CT), endobronchial ultrasonography (EBUS), endoscopic ultrasonography (EUS), mediastinoscopy. Agreement between cTNM and pTNM (according to 1997 TNM classification) was analyzed.

Results: 166 cases (characteristics in table 1). In table 2, concordance between cTNM and pTNM. cTNM and pTNM matched in 80 cases (48,2%), understaging occurred in 5 cases (3%) and overstaging in 81 (48,8%). But in most cases, this lack of agreement would not suppose changes in the therapeutic decision, just in 21 cases (12,5%) the cTNM carried out a wrong therapeutic procedure (18 N2 found in thoracotomy and 3 T4 unrespectable). TC and PET-TC used in all cases, EBUS in 35, EUS in 2 and mediastinoscopy in 3. In N staging, PET-CT was cN0 in 133 cases (where 7 were pN2, 5,2%) and cN1 (21 cases, 25,8%). We performed 35 EBUS (33 cN0, 2 cN1) and final pN was N2 in 3 cases (FN rate 8,5%).

Conclusions: 1. Low agreement between cTNM and pTNM (48,2%), but only in 12,5% of cases would suppose a change in the treatment. 2. 25% of pN2 when cN1 by PET-CT (EBUS should be done). 3. When EBUS negative for N2, only 8,5% pN2.

P2752

Prevalence of silent brain metastasis (BM) in the initial staging of non-small cell lung carcinoma (NSCLC)

L. Marzelli PariEspinoza, Daniel Huertas Almela, Susana Padrones Sanchez, Samantha Aso Gonzalez, Antoni Rosell Gratacos, J. Ignacio Martinez Ballarin, Jordi Dorca Sorgatul, Nuria Gonzalez Calzada. Respiratory Diseases, Hospital Universitari de Bellvitge, Barcelona, Spain

Introduction: Positron emission tomography (PET) can detect up to 15% of distant metastases in lung cancer, but it has a low sensibility in detecting BM.Guidelines recommend performing MRI only if there are neurological symptoms (NS). Our aim was to assess the role of MRI in detecting silent BM in the initial staging of NSCLC.

Material and methods: Retrospective analysis of new cases of NSCLC without distant metastases in lung cancer, but with a low sensibility in detecting BM.Guidelines recommend performing MRI only if there are neurological symptoms (NS). Our aim was to assess the role of MRI in detecting silent BM in the initial staging of NSCLC.

Results: MRI was made in 95 patients with NSCLC. 39%,40% and 21% had squamous cell carcinoma, adenocarcinoma and other histology respectively.

20%, 21% and 59% were stage I, II and III respectively BM were diagnosed by MRI in 11,6% (11/95) of the patients, and six of them (6/95, 6,35%), did not present NS.A stratified binary logistic regression analysis showed that there were not any clinical variable associated with the presence of silent BM in the asymptomatic subgroup, whereas central tumours (p=0,005) and ADK (p=0,01) were associated to BM in patients with NS. In both subgroups: staging, SUVm, tumour size and lymph nodes were not statistically indicative of BM.

Conclusions: Prevalence of silent BM at initial staging was 6,35%. Neither clinical nor radiological variables could predict silent BM. We concluded MRI is justifised as a routine procedure in NSCLC patients without BM in the PET. Partially funded by SOCAP.
P2753
Assessment of physical functioning in surgical candidates with non-small cell lung cancer: Preliminary comparison of performance status to symptom-limited cardiopulmonary exercise testing
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Background: Performance status (PS) scoring systems are used routinely by clinicians to guide management of patients with non-small cell lung cancer (NSCLC). However, PS scoring systems are subjective with poor inter-rater reliability and do not provide an objective measure of functional status. The aim of this study was to compare the variability in an objective measure of cardiopulmonary fitness (VO2peak) among surgical candidates with histologically confirmed NSCLC across different PS categories as assessed by the Eastern Cooperative Oncology Group (ECOG) Score.
Methods: Using a cross-sectional design, 389 subjects underwent an incremental cardiopulmonary exercise test with expired gas analysis to determine VO2peak prior to surgical resection.
Results: Mean VO2peak significantly declined across increasing ECOG categories (Table 1). There was a wide range in VO2peak in each ECOG category with similar ranges in VO2peak within groups, in particular in subjects classified as ECOG 1 and 2.

Table 1. Comparison of VO2peak to ECOG PS in NSCLC

<table>
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<tr>
<th>ECOG</th>
<th>VO2peak (ml kg–1 min–1)</th>
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<tbody>
<tr>
<td>0</td>
<td>29.6 ± 11.2</td>
</tr>
<tr>
<td>1</td>
<td>17.2 ± 4.5</td>
</tr>
<tr>
<td>2</td>
<td>15.0 ± 3.7</td>
</tr>
<tr>
<td>3</td>
<td>13.5 ± 3.1</td>
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Conclusions: VO2peak may provide a more sensitive evaluation of physical functioning than ECOG. Accurate assessment of functional status may have important implications for mortality risk and therapeutic management in the oncology setting.

P2754
Comparison of predictive respiratory function parameters of lung cancer patients after RFA procedures and diagnosis with postoperative complications and relation with mortality and morbidity
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Introduction and aim: Lung cancer with COPD increases surgical morbidity and mortality. In this research, non-small cell lung cancer (NSCLC) patients with/without COPD were investigated: 1. When preoperative predictive respiratory function parameters take place during postoperative period? 2. Which parameters are more valuable as a predictor of morbidity and mortality? Methods: This research was planned in a prospective manner. 46 NSCLC patients having pulmonary resection were grouped into 2. Group A: 23 moderate COPD patients. Group B: 23 non-COPD patients.
We checked patients for respiratory function tests, DLCO and arterial blood gases. Group A was also checked for ventilation/perfusion scintigraphy and VO2max.
We calculated predictive preoperative FEV1 and DLCO. We repeated respiratory function and DLCO tests during postoperative 1st, 3rd and 6th months.

Results and conclusion: There wasn’t any significant difference between 2 groups over demographic datos, operative skill, stage of cancer and type of resection. (p>0.05) Morbidity and mortality rates of Group A were significantly higher than Group B. Group A patients reached predicted results in 1st month and FEV1, DLCO results gained at 6th month were higher than predicted. In both groups, especially in Group B, best remarkable indicator for prediction of postoperative complications was DLCO%
Every patient going on pulmonary resection, should be tested for DLCO for determination of postoperative complication risk. It should not be forgotten that parameters checked for preoperative evaluation (FEV1% and DLCO%) are not always enough for decision of surgery.

P2755
Effect of adjuvant chemotherapy on lung function in early stage NSCLC
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Introduction: Pulmonary function can decline after induction chemotherapy and be predictive of perioperative complications in NSCLC. However, the influence of adjuvant chemotherapy on lung function is underdetected.
Methods: In a phase 2 trial on adjuvant therapy (TREAT), 132 patients with R0 resected NSCLC stage IB-IVN3, were randomized to 4 cycles Cisplatin/Vinorelbine (CVb, n=65) (C 50 mg/m² d1+8; Vb 25 mg/m² d1,8,15,22) 4 weeks or to 4 cycles Cisplatin/Pemetrexed (CPx, n=67) (C 75 mg/m², P 500 mg/m², d1 q3 weeks. Pulmonary function tests (forced expiratory volume in 1 s [FEV1], vital capacity [VC], total lung capacity [TLC], diffusing capacity [DLCO], blood gas analyses [BA]) were analyzed before and 30 days after therapy. Parameter changes were calculated (Δ-mean differences) and statistically analyzed.

Results: Overall, VC increased significantly (Δ+200 ml, n=47, p<0.0001), while TLC did not change significantly (Δ+220 ml, n=41, p=0.174). For CPx, FEV1 increased significantly (Δ+150 ml, n=47, p=0.0017), but not for CVb (Δ 3 ml, n=30). DLCO decreased only for CVb (-8%, n=6) but not for CPx (Δ-3%, n=17) (p=0.58). BGA did not change (p=0.99). In a Cox regression analysis, baseline lung function did not influence treatment failure (time until withdrawal from therapy due to adverse events, relapse, death, treatment refusal, non-compliance).

Conclusions: Adjuvant chemotherapy does not result in a decrease of lung function parameters but in a significant VC increase, probably due to ongoing postoperative improvement. Still, a non-significant difference between a DLCO decline under CVb but not for CPx warrants further attention. Moreover baseline lung function parameters do not impact treatment failure.
FEVI and DLCO had a significant correlation (R=0.376 p<0.001). The same analysis for both groups showed that FEVI and DLCO correlated better in ICT (R=0.630 p<0.03) than in NCT (R=0.244 p<NS). In NCT group, 10 from 14 analysis for both groups showed that FEV1 and DLCO correlated better in ICT. In ICT group, FEV1 and DLCO had a significant correlation (R=0.376 p=0.009). The same correlation was observed in NCT group. The mean (SD) age of patients was 69 (11) years. No adverse event was observed with both methods. Conclusion: FNA of palpable supravacular lymph nodes using clinical examina-
tion among patients with suspected lung cancer is a safe, cost-effective and as
accurate as US guided method.

P2762
CT guided biopsy: Predictors of outcome and complication rate
Rahuldeh Sarkar1, Amir Balawala1, James Jamieson-Young1, Andrew Wight1, Elspeth Partridge2, Marta Babores 1.

Aim: To compare the accuracy of FNA of palpable supravacular lymph nodes using palpation and ultrasound (US) among patients with suspected lung cancer.

Methods: Over a 30 month period (6/2008 – 12/2010) we examined 71 con-
secutive patients (54 males, 64.3±11.5 years) suspected for lung cancer with palpable supravacellular lymph nodes. All patients underwent US and palpation guided FNA at the same time. Samples were studied by immunohistochemical analysis.

Results: Sixty-four out of 71 patients had positive cytology by US (sensitivity: 93%) while the sensitivity of palpation was 90% (62/69). Seven patients under-
went surgical sampling of lymph nodes and the diagnoses were: 3 patients with adenocarcinoma, 2 with small cell lung cancer (SCLC) and 2 M. tuberculosis. Cytological diagnoses by FNA were: SCLC (23 patients), adenocarcinoma (22), squamous (7), undifferentiated non-small cell lung cancer (NSCLC) (6), unknown origin (2), lymphoma (2), sarcoidosis (1), and large cell carcinoma in 1 patient with NSCLC TNM classification was: stage IIB (24) and IV (12). Patients with SCLC demonstrated: limited (16) and extensive disease (7). No adverse event was observed with both methods.

Conclusion: FNA of palpable supravacular lymph nodes using clinical exami-
nation among patients with suspected lung cancer is a safe, cost-effective and as
accurate as US guided method.

P2763
Mediastinoscopy necessary in patients with negative EBUS-TBNA – A challenge to the ESTS Guidelines for staging of lung cancer
Mark Krasnik 1, Peter Vilmann2, Felix Herth3.

Objective: Mediastinoscopy is the golden standard for mediastinal staging of lung cancer. The aim of the present study was to examine whether mediastinoscopy may be avoided if a standardized EBUS-TBNA procedure using the same criterias as recommended mediastinoscopy was performed.

Methods: Patients with known or suspected lung cancer underwent a standardized EBUS-TBNA procedure using the same criterias as recommended mediastinoscopy. Both patients with EBUS-TBNA from station 4 R, 4L, and 7 without cancer were further referred for a VATS/thoracotomy.

Results: A total of 76 out of 95 consecutive patients, 48 males, 28 females were enrolled. Mean age 65 years (range 40-85). The mean sizes of the lymph nodes in all 3 stations were 9mm (range 2 - 35mm). The final primary diagnosis was cancer in 67 patients and benign diagnoses in 8 patients. In 4 patients mediastinal metastases were found by surgery (5%). One patient had a metastasis in station 4 R and 2 patients in station 5 and one patient in station 6. The NPV was 0.95 and with a specificity of 1.

In total the false negative rate of EBUS-TBNA in mediastinal staging of lung cancer was 4 out of 67 (6%).

Conclusions: The results of the present study seem to challenge mediastinoscopy as the gold standard. When EBUS-TBNA is performed under the same standard- ized conditions as described by the ESTS guidelines for mediastinoscopy with demonstration of lymphatic tissue from relevant lymph node stations, our study shows that very little, if anything, is gained by an additional mediastinoscopy and can be avoided.

P2764
Small cell lung cancer and thoracic lymph nodes metastatic involvement: A correlation
Vanja Kojadinovic Ostic, Zdravko Kojadinovic, Goran Djedanic, Palmodontology, Institute for Lung Diseases of Vojvodina, Sremska Kamenica, Serbia.

Aim: To determine the frequency of lymph node metastases depending on the lung cancer size.

Methods: A total of 136 lung resection samples obtained on surgery of the lung cancer patients, 114 males and 22 females, at the mean 54.8 years of age.

Results and discussion: Squamous carcinoma was the most frequent lung cancer type (66.9%), followed by adenocarcinoma (27.2%), while small-cell (4.4%) and largest (1.2%) cancer types were more rarely found. Metastatic involvement of the lymph nodes was discovered in 80 (56.7%) of 136 examined lung resection samples. The total of 489 thoracic lymph nodes were examined and metastases found in 207 (40.3%). The tumors sized 1.1-2 cm metastasized in 47% of the lymph nodes; the tumors sized 2.1-3 cm involved 32.7% of the lymph nodes by metastases; the tumors sized 3.1-4 cm metastasized in 36.3% of the thoracic lymph nodes; the tumors sized 4.1-5 cm involved 36% of the lymph nodes by metastases; the tumors in the size of 5.1-6 cm metastasized in 28.6% of the lymph nodes while those of over 6 cm in diameter involved 69% of the lymph nodes by metastases.

Conclusion: The number of lymph nodes involved by metastases does not increase with the size of the tumor of up to 6 cm, however, a further increase of the tumor size (over 6 cm in diameter) significantly increases the number of metastatic lymph nodes.
Table 2

<table>
<thead>
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<th></th>
<th>PTX</th>
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<tr>
<td>Hemorrhage</td>
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<td>No</td>
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<tr>
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<td>15</td>
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</tr>
</tbody>
</table>

Conclusion: Good pick up rate with complications well within acceptable standards were achieved in our study population. Depth of the lesion correlated well with pneumothorax and hemorrhage while size correlated with pneumothorax. Size was also a good predictors of conclusive biopsies.

P2763

The frequency and significance of radiologically detected indeterminate pulmonary nodules in patients with colorectal cancer

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Background: This study aims to investigate the frequency and significance of indeterminate pulmonary nodules in patients with non-metastatic CRC.

Methods: We retrospectively evaluated 1344 patients with CRC who underwent thoracic CT scans between the years January 2003-December 2009. Those with evident metastatic disease or already known to have pulmonary malignancies were excluded.

Results: Among all patients assessed, 55 (0.4%) of them had nodules that met the criteria of indeterminate pulmonary nodule. We analyzed the cases by size and number of nodules. A multivariable analysis demonstrated that indeterminate pulmonary nodules with irregular border (p<0.002), parenchymal localization (p=0.016) and being multiple in number (p=0.006) were predictors of metastatic disease.

Conclusion: The characteristics of indeterminate pulmonary lesions in CRC cases with no evidence of metastasis elsewhere have to be defined more comprehensively. We believe that for accurate decision of the frequency for follow-up interval further studies are required.

286. Palliation and morbidity in lung cancer patients

P2764

Sleep quality, quality of life and their correlative factors in lung cancer patients

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Objectives: To investigate the sleep quality and quality of life in patients with lung cancer.

Methods: We evaluated the sleep quality and quality of life of 98 lung cancer patients in our hospital by Karnofsky performance status (KPS), the Pittsburgh sleep quality index (PSQI) and the European organization for research and treatment of cancer quality of life questionnaire-core 30 and lung cancer module (EORTC QLQ-C30 and LC13). Then the newly diagnosed patients who had not received any treatment before were reevaluated after a month from the time of diagnosis or the first episode of treatment.

Results: The responding rate was 59.8%, and the rate of follow-up in newly-diagnosed patients was 51.5%. Evaluating performance status of lung cancer patients by KPS, 76.8% of them were considered to be able to keep on their normal life or work. The KPS of younger or better educated patients was better than that of older or lower educated ones. Evaluating sleep quality in lung cancer patients by PSQI, 45.9% were classified as poor sleepers. Unmarried patients, patients with college education used sleep medicine more frequently than married patients or patients with primary or high school education. Sleep efficiency was lower in patients with complications than those without complications. Evaluating quality of life in lung cancer patients by EORTC QLQ-C30, Seniles had better emotional and social function and less financial problems than non-senile patients.

Conclusions: Sleep disturbances did exist in patients with lung cancer, which had a great impact on their quality of life. KPS was still one of the most important factors that influenced quality of life in lung cancer patients.

P2765

Preoperative anxiety may affect the quality of life and health outcome of the patients that undergo thoracic surgery

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Purpose: Increased preoperative anxiety level may lead to adverse outcomes. The purpose of this study was to assess the relationship between the quality of life and preoperative anxiety during the four-week preoperative period in patients scheduled to undergo thoracic surgery.

Patients and methods: The study population consisted of 100 patients, 52 men and 48 women scheduled to undergo thoracic surgery. The average of age was 56.1±15.60 years. After providing informed consent, they were asked to answer a questionnaire, 12 to 15 hours prior to the scheduled thoracic surgery operation. The questionnaire included questions on demographics and incorporated the State Anxiety Inventory and SF-36 scales.

Results: Statistical analysis revealed that women (p=0.023), unemployed patients (p=0.01) and patients that were to be submitted to a mediastinoscopy (p=0.001) had elevated anxiety levels. Deterioration of several parameters relative to the quality of life was found to be related to increased anxiety levels. Limitations in work capability or other everyday activities as result of mental health problems (p=0.006), low vitality (p<0.001), bad general mood (p<0.001), deteriorated general health (p<0.001) and general mental health (p<0.001) were associated with preoperative anxiety. No differences were found in anxiety level between lung cancer and non-cancer patients.

Conclusions: This study showed an inverse proportional correlation between preoperative quality of life and anxiety during a period of four weeks prior to a thoracic surgery operation. Appropriate pharmaceutical and psychological support may improve patients’ anxiety status.

2766

Religiosity and depression of patients with lung cancer

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The relationship between depression and religiosity of patients with lung cancer is not yet explored.

Aim: To examine possible association of religiousness and depression of patients with lung cancer and the relationship between religiosity and depression with sociodemographic data.

Subjects and methods: Forty-four patients with lung cancer were consecutively included. The Strength of Religious Faith Santa Clara questionnaire was used for assessment of religiosity, and for measuring depression the Center for Epidemiological Study of Depression (CES-D). Overall religiosity was measured with 5-point Likert scale.

Results: The mean age of 59-54 years, mean overall religiosity, SCSCOF 27.8, CES-D 17.9. In 43.1% meets the criteria for diagnosing depression. In logistic regression analysis the only significant predictor of depression was less common frequency of going to church. Depression is more pronounced in women and in religiosity there is no difference by gender. Significant differences in the items that measure loneliness, sadness, feelings of fatigue and anxiety are more pronounced in women.

Conclusions: Higher frequency of going to church predicts lower depression rate in the group of patients. Strength of faith and general assessment of religiosity were not significant predictors of depression which is not in accordance with the findings other studies. These differences might be associated with factors specific for lung cancer and may be effect of gender, and should be explored in further studies.

References:
P2776
Potential role of antidepressants as part of anticancer therapy
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Antidepressants are widely used as part of adjuvant analgesic therapy. Since in vitro studies show that antidepressants have potent antitumor properties, it raised the possibility of a potential role as a part of anticancer therapy.

Aim: To estimate possible favorable effect of Mianserin (M) in lung cancer patients: (1) potential influence on survival due to anticancer properties, (2) improvement of patients psychological pattern and health-related quality of life (HRQoL).

Methods: Two groups of advanced NSCLC patients were included: 52 pts treated with CT and without M and 60 pts treated with BSC with or without M. Differences in response rates (only for CT treated group), in overall survival (OS) and HRQoL, (based on EORTC QLQ-30 and QLQ-LC 13) with within (sub)groups were evaluated.

Results: The RR difference within the CT subgroups treated with or without M, was not statistically significant: 8/24 (33.33%) vs 6/28 (21.43%). There was significant difference in median OS with 95% CI for the different treatment subgroups (only BSC, BSC plus M, only CT and CT plus M), respectively: 6 (5-6), 7 (6-8), 8 (7-10) and 10.5 (10-13) months (p=0.89;10-15). Pts receiving M (and CT or BSC) had significantly better OS (p=0.0012). CT treated pts receiving M had significantly better survival comparing to those not receiving M (p=0.0015). BSC treated pts receiving M had also significantly better survival than those without M (p=0.003). M treated subgroups had significantly higher scores of QLQ-C30 and LC13 i.e. better HRQoL, as well.

Conclusion: Benefit of antidepressants as part of anticancer therapy noted should be further investigated in larger patients population studies with different antidepressants.

P2768
Frequency of thromboembolic events in patients with lung cancer at the time of diagnosis and in the course of disease
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Background: Clinicians are frequently confronted by thromboembolic events (TEE) in patients with lung cancer. Early pulmonary embolism (within the first 3 months after primary diagnosis) is regarded as a negative prognostic factor. However, the benefit of a prophylactic anticoagulation has not been evaluated so far. Lung cancer itself as well as certain chemotherapeutic agents are considered to be independent risk factors for TEE.

Methods: Two groups of advanced NSCLC patients were included: 52 pts treated with CT and without M and 60 pts treated with BSC with or without M. Differences in response rates (only for CT treated group), in overall survival (OS) and HRQoL, (based on EORTC QLQ-30 and QLQ-LC 13) within (sub)groups were evaluated.

Results: The RR difference within the CT subgroups treated with or without M, was not statistically significant: 8/24 (33.33%) vs 6/28 (21.43%). There was significant difference in median OS with 95% CI for the different treatment subgroups (only BSC, BSC plus M, only CT and CT plus M), respectively: 6 (5-6), 7 (6-8), 8 (7-10) and 10.5 (10-13) months (p=0.89;10-15). Pts receiving M (and CT or BSC) had significantly better OS (p=0.0012). CT treated pts receiving M had significantly better survival comparing to those not receiving M (p=0.0015). BSC treated pts receiving M had also significantly better survival than those without M (p=0.003). M treated subgroups had significantly higher scores of QLQ-C30 and LC13 i.e. better HRQoL, as well.

Conclusion: Benefit of antidepressants as part of anticancer therapy noted should be further investigated in larger patients population studies with different antidepressants.

P2777
Study of the lung cancer patients on hemodialysis (HD) in Japan
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Introduction: Early stage lung cancer in patients with end-stage renal disease are often detected by routine chest radiography on hemodialysis (HD) filtration. It is general that standard treatment for hemodialysis patients with lung cancer are not performed because guideline for lung cancer in HD patients is not established yet. Thus, clinicians have difficulty in treating HD patients even though early stage lung cancer is detected.

Method: We retrospectively analyzed 17 HD patients with lung cancer between April 2004 and September 2010. Patients’ characteristics, histology and stage of lung cancer, treatment and outcome were evaluated.

Results: A total 17 patients (13 male, 4 female) were eligible in this study. The median age was 72 years (range 54-90). Eleven patients of non-small cell lung cancer (NSCLC) and 1 small cell lung cell cancer (SCLC) had histological or cytological confirmation and 3 were unknown. They consist of 3 stageI, 1 stageII, 8 stageIII and IV. As for treatment, operation was taken in 3, chemotherapy alone and radiochemotherapy were received in 4 and 1. Nine patients did not receive any treatment since they are too old, had a poor performance status or considered to be intolerable by attending physicians.In terms of chemotherapy, hepatic excretery-anti-cancer drugs were used in all the 4 patients. No severe adverse events related-treatment was seen in this study.

Conclusion: Guideline for HD patients with advanced stage lung cancer should be established.

P2772
Antibiotic prophylaxis in chemotherapy-induced neutropenia in lung cancer patients
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Introduction: Chemotherapy-induced neutropenia can potentially cause fatal infections in cancer patients. Human granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are recommended as prophylaxis. Alternatively, prophylactic antibiotics have been administered.
P2773
Hematological toxicity associated with gemcitabine/cisplatin in elderly non-small cell lung cancer patients

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Introduction: Chemotherapy regimen gemcitabine/cisplatin is indicated in the treatment of non-small cell lung cancer (NSCLC), stage IIIb and IV with good performance status (according to leading National Comprehensive Cancer Network (NCCN) guideline).

Aim of the study: To compare the hematological toxicity of gemcitabine/cisplatin between elderly and patients younger than 65 years of age.

Patients and methods: In our study we observed 235 chemotherapy-naive patients divided into two groups according to their ages: younger than 65 years of age (194 patients) and patients older than 65 years of age (59 patients). Both groups of patients had received chemotherapy regimen: gemcitabine (1000mg/m² iv. day 1, day 8, and day 15) and cisplatin (100mg/m² iv. day 1, day 8) in weeks 1-3 and 4-6.

Results: Hematological toxicity were registered in 26/194 (13.4%) younger patients compared to 15/59 (25.3%) older patients. Statistical analysis showed significant differences in appearance of hematological toxicity in elderly patients (p=0.046). Patients who had received chemotherapy regimen: gemcitabine (1000mg/m² iv. day 1 and day 8),and cisplatin (50mg/m² iv. day 1 and day 3) in weeks 1-3 and 4-6.

Conclusion: According to our results, there is no statistically significant difference between the two groups of patients in appearance of anemia, leukopenia, thrombocytopenia, but generally hematological toxicity is more often in elderly patients.

P2774
A study comparing the efficacy, quality of life and toxicity of cisplatin-paclitaxel to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer in the Indian Scenario

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Background: The present study was designed to evaluate the efficacy, toxicity and quality of life of the regimen of carboplatin plus paclitaxel (investigational arm) versus the reference regimen of cisplatin plus etoposide for the treatment of advanced or metastatic non-small-cell lung cancer in the Indian Scenario.

Patients and methods: A total of 50 patients were enrolled, 25 on arm A (cisplatin 25 mg/m² and etoposide 100 mg/m²) and 25 on arm B (carboplatin AUC= 6 mg/ml min and paclitaxel 225 mg/m²), with cycles repeated every 3 weeks. The arms were well balanced with respect to age, performance status, weight loss, stage of disease and disease measurability.

Results: The objective response rate (ORR) was 76% on arm A compared with 72% on arm B (P = 0.74). The most prevalent toxicities were alopecia, nausea and vomiting in both the arms. Leukopenia and neurological toxicity (neuro-sensory+ neuro-motor) occurred at a higher rate in arm B than in arm A without statistical significance. 60% patients in arm B had statistically significant improvement in quality of life as compared to only 20% patients in arm-A (P=0.008)

Conclusion: There was no statistically significant difference in efficacy and toxicity for carboplatin-paclitaxel compared with cisplatin-etoposide. However, there was a statistically significant improvement in quality of life with the carboplatin-paclitaxel regimen.

P2775
Achieving better therapeutic results by education and telephone counseling for lung cancer patients undergoing scheduled chemotherapy regimens

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Results:

8th Pulmonary Clinic, Hospital for lung cancer patients undergoing scheduled chemotherapy regiments

P2776
Can exhaled nitric oxide (FeNO) predict radiotherapy-induced lung toxicity in lung cancer patients?  

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A strong increase in FeNO after radiotherapy (RT) for lung cancer may predict RT-induced lung toxicity. We aimed to describe the time-course of FeNO till 7.5 months after 3D conformal RT, and assess the relationships between FeNO and respiratory symptoms, CT scan changes or dosimetric parameters.

FeNO was measured before RT, and 4, 5, 6, 10 weeks, 4 and 7.5 months after the beginning of RT.

Most of the 65 patients were males (74%), had squamous cell carcinoma (48%), and stage III disease (72%). 41 patients had sequential chemo-RT, 20 had concurrent RT and chemotherapy, and 4 had only RT.

Eleven patients (17%) complained of respiratory symptoms after RT. Mean FeNO was a little lower before RT (14.3 (7.2) ppb) than at 7.5 months (18.2 (12.5) ppb + 30% (8%), p=0.05). Between 4-10 weeks, 51-61% of patients showed non-significant changes in FeNO (< 5 ppb), whereas 13-18% showed increased FeNO compared to pre-RT values. Mean changes in FeNO were not different in patients with or without respiratory symptoms. Three patients (5%) had a >2-fold increase in FeNO, at 4 and 5 weeks. All three showed radiation-pneumonitis images at 3-4 months but only two had respiratory symptoms. The sensitivity and specificity of FeNO for the diagnosis of RT-induced symptoms were 18% and 84% for a >5 ppb increase, and 18% and 98% for a >2-fold increase. There was no correlation between dosimetric parameters and changes in FeNO. There was no correlation between absolute values or variations in FeNO and CT scan changes after RT.

Conclusion: Serial FeNO measurements during RT cannot separate patients who will develop or stay free of radiation pneumonitis with sufficient accuracy.

P2777
Cetuximab maintenance therapy – How long should we proceed? A case report

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The continuation of an active therapeutic agent for extended duration following frontline induction chemotherapy as maintenance therapy can improve overall survival. The Gemtex IV trial compares a platinum-containing doublet vs. a platinum-free sequential chemotherapy with docetaxel and gemcitabine, both arms in combination with cetuximab until progression. However, a useful predictive marker for maintaining an EGFR antibody treatment still does not exist.

We report about a 56-year-old female Caucasian patient with multiple pulmonary

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lesions and diagnosis of a bronchioalveolar carcinoma. She was at good perfor-
mance status (ECOG 0), without relevant comorbidities and a smoking history of
35 pack-years. EGFR mutation analysis showed an insertion in exon 20 of the EGFR-
genre. Within the Gemtix IV trial 4 cycles of carboplatin/gemcitabine/ cetuximab
were given. Toxicity was a grade III neutropenia and a grade 1 rash without
itching. A total number of 16 cycles cetuximab were completed until therapy was
stopped on patient’s request. After six weeks, tumor progression was documented,
resulting in a PFS of 12.5 months. In the course, the patient did benefit from
another chemotherapy, but not from an EGFR-TKI (erlotinib). OS was 32 months.
In our study tumor progression was not seen after stopping cetuximab mainte-
teinance therapy. This could indicate a significant antitumor activity of the EGFR
antibody in this patient. Biomarkers or clinical selection criteria should be identi-
fied that allow to predict patients benefit from cetuximab maintenance therapy and
avoid such “rebound phenomenon” or unneeded maintenance treatment.

P2778
Clinical predictors for long-term benefit of cetuximab maintenance therapy –
Single center subanalysis of the GEMTAX IV trial
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Germany

The Gemtix IV trial compares a platinum-containing doublet (Arm B) vs. a
platinum-free sequential chemotherapy with docetaxel and gemcitabine (Arm A),
both arms in combination of cetuximab until progression. Our center included
59 patients in the GEMTAX IV trial so far. From them 9 patients received cetuximab
for 10 or more cycles. We analyzed clinical markers in relation to long term
therapeutic benefit from cetuximab.

A median of 13 cycles (10-15) with cetuximab was administered; mean age was
63 years (53-75). The relations of male to female, non-squamous to squamous his-
tology, and treatment regimen Arm A to Arm B were 2:1 respectively. The median
progression free survival was 10 months (8-13) and overall survival 22 months
(9-33) so far. Seven of 9 patients developed an acne-like rash within 5 weeks of
cetuximab treatment. Eight of 9 patients were former or current heavy smoker.

Patients with long-term benefit from cetuximab maintenance after induction
chemotherapy were mostly male, former or current smoker, of non-squamous
histology and presented rash early. In accordance with data from the FLEX trial,
to monitor rash could be helpful on identifying patients who could benefit from
cetuximab maintenance therapy.

P2779
Clinicopathologic characteristics of primary bronchial cancer metastasizing
to the brain
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Brain metastasis is one of the most important factors influencing the quality of life
in lung cancer patients with metastatic disease.

We analyzed the clinicopathological data of 163 lung cancer patients with brain
metastasis (96 men, 67 women). The brain metastasis was diagnosed either by CT
(n=119) or MRI (n=44). The lung cancer was diagnosed according to bron-
choscopy, surgical resection VATS biopsy or transtoracic needle biopsy. The lung

tumor was in the right lung. The upper lobes were concerned in 92 cases (56.4%).
The histological distribution was the following: 67 adenocarcinomas, 43 small cell

carcinoma, 2 atypical carcinoid tumors and 16 malignant tumors.

When compared small cell lung cancer to adenocarcinoma, the proportion of early
metastasis was much higher. In our study the upper lobe adenocarcinoma localized
to the upper lobes, and among them the proportion of early metastasis was very
high. According to our results, especially in case of upper lobe adenocarcinoma,
the exclusion of intracranial metastasis by brain MRI is highly desirable before
surgical resection of lung cancer.

P2780
Survival of lung cancer patients with bone metastases
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of Novi Sad, Novi Sad, Vojvodina, Serbia

The presence of metastatic diseases in lung cancer patients is common in everyday
clinical practice. The aim of this study is to establish frequencies of bone metastases in our patients
(pts). and their association with other metastases (as brain, liver etc.) and to
investigate their survival and treatment effects.

Methods: The data were collected from the Hospital Registry. The investigation
was carried out in non operated patients. It included 1197 newly discovered lung
cancer patients., 71 (6.93%) patients had bone metastases. In the moment of the
dates analysis, 62 (87,3%) were dead, and the mean survival was 2.5 month
(survival range 0.1-13month). Solitary bone metastases have 25 (35,2%) patients.,
and multiple bone metastases have 46 (64,8%) patients, while bone and other
metastases were found in 37 (52,1%) patients. Only 14 (19,7%) patients were

treated with bisfonatons therapy, and their mean survival was 2 months.

Conclusion: Lung cancer patients with bone metastases, usually associated with
other metastases, achieved a wary poor survival. Neither the paliativ irradiation of
solitary metastases nor bisfonatons therapy improved the survival of lung cancer
patients.

Endobronchial lesion obliterating the right intermediate bronchus was observed
at fiberoptic bronchoscopy. Histopathologic examination of the mass was diagnosed as
carcinoid tumor. Serum and urine 5-hydroxy indol acetic acid (5-HIAA) levels were
within normal range. Thoracolumbar spinal magnetic resonance imaging (MRI)
revealed pressure upon the medulla spinalis and the patient underwent laminotomy
and thoracic hemilaminectomy operation. The patient received chemoradiother-
apy diagnosed as atypical carcinoid tumor infiltration with T6 vertebra excisional
biopsy.

P2782
Complete regression of eyeball metastasis secondary to non-small-cell lung
cancer with intravitreal cisplatin and vinorelbine therapy
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To report a case of a complete regression of intraocular metastasis secondary to
non-small-cell lung cancer with intravitreal cisplatin and vinorelbine therapy

Purpose: To report a case of a complete regression of intraocular metastasis
secondary to non-small-cell lung cancer (NSCLC).

Methods: Retrospective case review of a 61-year-old female patient treated with
intravitreal cisplatin and vinorelbine therapy for posterior segment of eyeballs
metastases secondary to NSCLCs. Best corrected visual acuity, fluorescein angiography
and computed tomography with contrast intensification were compared during the
3-month treatment period.

Results: After the 4-cld cycle of chemotherapy (intravitreal cisplatin and vinorelb-
ne) the best corrected visual acuity had improved to 20/40 from 20/100 and 2
elevated choroidal mass in the superotemporal and inferotemporal quadrants of
the right eyeball and 1 mass in the lower-inside quadrant of the left eyeball
had completely disappeared. The retina and a retinal pigment epithelial layer were
normal.

Conclusion: Combining intravitreal cisplatin and vinorelbine could be the optimal
treatment form for patients with intraocular metastasis of NSCLC.
Nitrosoglutathione reductase inhibition in the airway epithelium may lead to lung cancer. Little is understood however, regarding the potential for engineered NOs to cause genotoxicity. The aim of this project was to use in vitro human epithelial airway-model (epithelial cell layer (16HBE14o-) cells with human monocyte derived macrophages (apical layer) and dendritic cells (basolateral layer), with different toxicological endpoints involved in NO-induced genotoxicity. Single- and multi-walled carbon nanotubes (SWCNTs/MWCNTs), as well as crocidolite asbestos fibres (CAFs) and DEPs caused no significant (p>0.05) cyto- toxicity (lactate dehydrogenase release) up to 0.04/mg/ml after 24hs. Significant increases (p<0.05) in both L8 and TNF-alpha levels at 0.05-0.04/mg/ml over 24hrs were observed in both the apical and basolateral layers for all NOs. The NO-cell driven mechanism in vitro cells were exposed to 1) 30 ppm NO in a sealed incubator; or 2) S-nitrosocysteine (SNOC) or cysteine (CYS) for 2d, 5d, or 10d, or 3) S-nitrosoglutathione (GSNO) for 2d, 5d, or 10d. Immunoblot. Active GTP-Ras was assayed in a Raf-1RBD-binding ELISA. Certain wt Ras S-nitrosylation and activation in the lung.

Background:
Throughout the project we aimed to determine whether decreased GSNO reductase promoter wt Ras S-nitrosylation and activation in the lung. We studied whether decreased GSNO reductase promotes greater in vitro lung cancer risk.

Methods:
Furthermore, GSNO can be tumorigenic by activating wild-type (wt) Ras proteins which are known to promote tumorigenesis and may not be a good strategy for asthma treatment, particularly in smokers.

Results:
While COPD induces an increase in systemic and bronchial oxidative stress in patients with associated lung cancer, the latter condition is related to greater content of proinflammatory cytokines and angiogenic factors in both blood and bronchi of the patients.

Conclusion:
Chronic airway inflammation such as that observed in COPD patients is a relevant contributor to lung cancer. Increased inflammation and oxidative stress levels have been shown in lung cancer lesions compared to non-tumor parenchyma.

P2786
Role of systemic and bronchial oxidative stress and inflammation in lung cancer predisposition in patients with COPD.

Nadirzah Marozkina, David Jones, Sean Yemen, Benjamin Gaston. Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, United States

Background:
Nitrosothiol (GSNO) is an endogenous bronchodilator. GSNO reductase (GSNOR) depletes airway GSNO; inhibitors are in development for asthma. However, GSNOR can be tumorigenic by activating wild-type (wt) Ras proteins which are known to promote tumorigenesis and may not be a good strategy for asthma treatment, particularly in smokers.

Methods:
Furthermore, GSNO can be tumorigenic by activating wild-type (wt) Ras proteins which are known to promote tumorigenesis and may not be a good strategy for asthma treatment, particularly in smokers.

Results:
While COPD induces an increase in systemic and bronchial oxidative stress in patients with associated lung cancer, the latter condition is related to greater content of proinflammatory cytokines and angiogenic factors in both blood and bronchi of the patients.

Conclusion:
Chronic airway inflammation such as that observed in COPD patients is a relevant contributor to lung cancer. Increased inflammation and oxidative stress levels have been shown in lung cancer lesions compared to non-tumor parenchyma.

P2787
Detection of patients with lung cancer out of a risk group by breath sample presentation to sniffer dogs.

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Background:
We evaluated airflow obstruction as a possible independent risk factor for lung cancer (LC) in patients with bronchial squamous dysplasia (SD).
P2788

A new possibility of process monitoring in lung cancer: Volatile organic compounds detected with ion mobility spectrometry to follow the success of the therapeutic process.

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Introduction: Lung cancer is mostly detected when it is already too late for surgery. But even when tumours can still be operated, there has not been a simple, convenient way of observing any follow-up parameters such as PSA in prostate cancer. With the non-invasive analysis of Volatile Organic Compounds (VOCs) in exhaled breath using ion mobility spectrometry (IMS) we get the chance to step up in this development.

Objectives: To develop a non-invasive technique of analysing new tumour markers in order to find a follow up biomarker for an improved monitoring of the treatment of lung cancer patients.

Methods: Exhaled breath from 33 lung cancer patients was collected and analysed with an IMS device before and after lung surgery. The patients were split into groups according to the tumour histology. Additional conditions such as COPD, medication and former radiation or parameters such as PSA in prostate cancer. With the non-invasive analysis of Volatile Organic Compounds (VOCs) in exhaled breath using ion mobility spectrometry (IMS) we get the chance to step up in this development. Furthermore, the results were statistically analysed.

Results: There were several peaks which showed differences between the pre- and post-surgery groups (such as “EV” normol: 0.062 in squamous cell carcinoma). Further results will be presented in box plots.

Conclusion: As the results show differences between the peaks before and after surgery, the analysis of VOCs in exhaled air might be a new non-invasive possibility of monitoring the process of lung cancer therapy.

In future research it would be interesting to carry out further investigations on long-term patient observations after defined time intervals.

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The research on early detection of lung cancer with exhaled volatile organic compounds

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We analyzed exhaled breath VOCs of 243 samples by SPME-GCMS system, including 88 samples of lung cancer, 70 samples of lung benign disease, 85 samples of health person, and further researched the sensitivitiy and specificity of the diagnostic models based on different combinations of special VOCs by applying statistical approaches, such as cluster analysis or stepwise discriminant analysis. In the end, we selected age, as well as 4 to 6 VOCs, as the diagnostic models for lung cancer, including 2,6-dimethylnaphthalene, palmitic aldehyde, nonadecyl alcohol, etc, basically with high sensitivity and specificity more than 85%. Take one model for example, which is consist of palmitic aldehyde, nonadecyl alcohol, 2,6-dimethylnaphthalene, age, and so on, its specificity is 94.9%, and 78.7% of early stage lung cancer patients were correctly identified, however, 31.9% of them were misclassificated to advanced stage. Therefore, this kind of diagnostic model could be applied to early diagnosis of lung cancer, but with poor effect to differentiate stages, which indicates that breath test diagnostic model for lung cancer might be one of the screening and early warning methods, although is not enough as a diagnostic model for lung cancer.

In future research it would be interesting to carry out further investigations on long-term patient observations after defined time intervals.

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Volatile organic compounds in lung cancer patients before and after tumour resection.

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Introduction: Ion mobility spectrometry (IMS) is a promising tool in the detection of volatile organic compounds (VOC) even in small amounts. Whether it can contribute to the diagnosis of non-small-cell cancers (NSCLC) has not been adequately evaluated. Breath analysis with IMS is based on the assessment of multiple volatile organic compound (VOC) peaks considered specific for the disease.

Objectives: We studied bronchoscopically obtained VOCs in exhaled breath with an ion mobility spectrometer coupled to a multi capillary column (MCC/IMS) in patients with NSCLC before and after tumour resection in order to find tumour specific VOCs.

Methods: In 8 patients with histologically proven NSCLC, gas samples were aspirated out of the lungs during the diagnostic bronchoscopy and after tumour resection. Gas samples were aspirated via a Teflon tube introduced in the working channel of the bronchoscope and assessed using IMS.

Results: We found 228 common peaks in the measured data. 17 of them were significantly different before and after surgery. 11 peaks could be found with a lower value after tumour resection whereas 6 had a higher value.

Conclusion: While in a former study (Poli D et al. Acta Biomed 2008; 79; Suppl 1: 64-72) using solid-phase micro-extraction no changes after lung cancer resection could have been found, IMS revealed a change in the composition of exhaled breath after surgery in our work. Therefore some VOC levels may have been influenced by the tumour and these VOCs can be detected by MCC/IMS.

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New contributions in the determination of volatile organic compounds (VOC) in lung cancer (LC).

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Introduction: Determination of VOC present in exhaled breath (EB) may be useful as a noninvasive diagnostic technique in LC.

Objective: To analyze the presence of VOC in the EB in two groups of subject: LC Group and Control Group.

Methods: Descriptive, observational study. LC Group: 29 patients with LC. Control Group: 40 healthy volunteers. (All accepted Informed consent). Breath samples were collected at lung residual functional capacity, with simultaneous sampling of ambient air using bioVOC devices. Analytical technique: Thermal desorption Markers Int. Gas chromatography (7890A) mass spectrometry (5975C_Hewlett Packard). VOC analyzed, see table 2. Compounds identified by means of reten- tion time + mass spectrum. Chromatographic column: DB1: 30mx0.25mmx1um (Hewlett Packard).

Results: We analyzed exhaled breath of 243 samples by SPME-GCMS system, including 88 samples of lung cancer, 70 samples of lung benign disease, 85 samples of health persons.

Conclusions: The research on early detection of lung cancer with exhaled volatile organic compounds.
Neutrophil elastase levels is higher in patients with lung cancer than chronic obstructive pulmonary disease

Neutrophil elastase (NE) is a specific serine protease and it is a modulator of inflammation. Systemic and pulmonary inflammation has been associated with both non-small cell lung cancer (NSCLC) and chronic obstructive pulmonary disease (COPD). Still, an exact role of NE in pathogenesis of NSCLC, COPD and in coexistence of both diseases is unknown. The aim of the study was to evaluate NE levels in NSCLC with and without COPD.

**Methods:** Serum and BAL fluid (BALF) levels of NE were measured by enzyme-linked immunosorbent assay (ELISA) in 28 patients with NSCLC, 20 patients with moderate COPD, 25 patients with NSCLC and moderate COPD (NSCLC/COPD) and 10 healthy non-smoking individuals (HI). Periferal blood and BALF were collected from each patient before any treatment.

**Results:** Serum NE levels were significantly higher in groups with NSCLC: NSCLC, NSCLC/COPD, compared to COPD or HI (620.6±77.5 ng/ml and 609.8±52.7 ng/ml vs 409.2±61.6 ng/ml and 243±23.9 ng/ml, P<0.05). BALF NE levels were significantly higher in NSCLC and NSCLC/COPD. Levels were significantly higher in NSCLC than in COPD and HI (1.47-fold, NSCLC/COPD (1.53-fold) compared to COPD (1.21-fold, P<0.05) or HI (basal level). Serum NE levels were correlated with the clinical/pathological status of patients with NSCLC.

**Conclusions:** Our data suggest a higher levels of NE both in NSCLC and NSCLC/COPD than in COPD or HI.

The expression of IL-5 in lung cancer tissue and its relationship with the expression of IL-5

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**Objective:** Some studies showed that high eosinophil infiltration in lung cancer tissues was associated an improved prognosis. And the other studies showed the high expressed of IL-5 in lung cancer cells. IL-5 has emerged as a main controlling tissues was associated an improved prognosis. And the other studies showed the expression of IL-5 was associated with better survival. So we studied the eosinophil infiltration and the expression of IL-5 in five tissue specimens from lung cancer patients and analyzed the correlation between the eosinophil infiltration and IL-5 expression of lung cancer tissue.

**Methods:** Eosinophil infiltration was detected by Immunohistochemistry in 45 lung cancer tissues and 36 corresponding normal lung tissues.

**Results:** There were high tissue eosinophilic infiltrations in 17 of 45 (37.78%) cases. In high eosinophilic infiltration cases, the counting of eosinophil in tumor tissue was significantly higher than that in corresponding normal tissues (P<0.05). In NSCLC, the rate of high eosinophilic infiltration cases was significantly higher than that of SCC (P<0.05). IL-5 was high expressed in all 45 cases and low expressed in corresponding normal tissues. Eosinophilic infiltration was not correlated with the expression of IL-5 in tumor cells (r=0.026, P=0.05).

**Conclusions:** There were high eosinophilic infiltrations of tumor tissues in some cases of lung cancer. Compared with SCC, the rate of high tissue eosinophilic infiltration cases of NSCLC was significantly increased. There was no relationship between the eosinophilic infiltration and the expression of IL-5 in lung cancer tissue.

**P2795**

Association of genetic polymorphisms of matrix metalloproteinase (MMP)14 to the susceptibility of non-small cell lung cancer

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**Background:** Matrix metalloproteinase (MMP)14 is a cell surface protease that displays a broad spectrum of activity against extracellular matrix components and promotes the invasion/metakasis of cells. MMP14 is overexpressed in NSCLC, and the level is correlated with poor survival. We investigated the MMP14 -165 TT genotype against GG/GT genotypes (an OR of 1.84, 95% CI 1.22-2.77, P=0.005), MMP14 +7096 CC genotype against TT/TC genotypes (an OR of 1.79, 95% CI 1.19-2.70, P=0.005), and MMP14 +8153 GA genotype against GG genotypes (an OR of 2.07, 95% CI 1.36-3.14, P=0.001).

**Methods:** Eighty-six newly diagnosed (nd) NSCLC patients in the lung cancer group were compared to 73 COPD patients using a Cyranose 320 (Smith Detection) electronic nose.

**Results:** The distribution of the genotype frequencies of MMP14 -165 (GT/G), MMP14 +7096 (T/C), and MMP14 +8153 (G/A) were significantly different between the lung cancer patients and the healthy controls. Logistic regression analysis revealed that higher odds ratios (ORs) for lung cancer were seen for individuals with MMP14 -165 TT genotype against GG/GT genotypes (an OR of 1.84, 95% CI 1.22-2.77, P=0.005). MMP14 +7096 CC genotype against TT/TC genotypes (an OR of 1.79, 95% CI 1.19-2.70, P=0.005), and MMP14 +8153 GA genotype against GG genotypes (an OR of 2.07, 95% CI 1.36-3.14, P=0.001).

**Conclusion:** A significant association between the polymorphisms of MMP14 gene and the susceptibility to NSCLC was demonstrated.

**P2796**

The expression and clinical significance of PD-L1+CD68+ macrophages in peripheral blood mononuclear cells of non-small cell lung cancer

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**Purpose:** To explore the role of PD-L1+ programmed death-1 ligand 1) CD68+ macrophages in peripheral blood mononuclear cells (PBMCs) of non-small cell lung cancer (NSCLC) by flow cytometry (FCM).

**Materials and methods:** 60 squamous cell carcinoma patients, 60 adenocarcinoma patients and 60 healthy controls were recruited in the study. PD-L1+CD68+ macrophages were isolated from PBMCs of the 180 persons with FCM.

**Results:** Squamous cell carcinoma and adenocarcinoma group had higher PD-L1+CD68+ macrophages expression compared to healthy controls (P<0.000) and PD-L1+CD68+ macrophages were isolated from PBMCs of the 180 persons with FCM.

**Conclusions:** Squamous cell carcinoma and adenocarcinoma group had higher PD-L1+CD68+ macrophages expression compared to healthy controls (P<0.000) and PD-L1+CD68+ macrophages were isolated from PBMCs of the 180 persons with FCM.
Magnolol-induced apoptosis is mediated through caspase-independent pathway. Reduced by Magnolol translocated from mitochondria to nucleus, suggesting that the production of caspase-independent pathway was involved in the apoptosis induced by Magnolol. The mitochondria potential of mitochondria in A549, H520 and H441 cells started to decrease within 6 hr after treatment with Magnolol at various concentrations, and the results showed that the mitochondria potential of mitochondria in A549 cells started to decrease within 6 hr after treatment with Magnolol at various concentrations, and the results showed that the concentration of IL-6 in BALF was slightly higher than that of serum IL-6, but not statistically different from that of PID patients. In patients with NSCLC, the concentration of IL-6 in BALF was higher than that of PID patients. We found that the concentration of IL-6 in BALF was higher than that of PID patients and normal controls (P < 0.01). The concentration of IL-6 in serum or BALF was not statistically different from that of PID patients. In patients with NSCLC, the concentration of IL-6 in BALF was higher than that of serum IL-6, but this difference was not statistically significant (P > 0.05). Serum IL-6 level was higher in NSCLC patients of advanced stages (stage IIIb and IV), as compared with that in NSCLC patients of early stages (stage Ia-IIb). BALF IL-6 level of NSCLC patients at different stages was not different. IL-6 level (in serum but not in BALF) of PID patients correlated with the serum concentration of C reactive protein (r=0.69).

Conclusion: IL-6 in BALF might be used as a marker for NSCLC. Serum IL-6 level might be an indicator for the stage of NSCLC. The serum IL-6 can also be measured by ELISA.

Methods: The concentration of IL-6 in serum or BALF of 82 NSCLC patients, 56 patients of pulmonary inflammatory diseases (PID) and 26 normal controls were measured by ELISA.

Results: The concentration of IL-6 in BALF of NSCLC patients was significantly higher than that of PID patients and normal controls (P < 0.01). The concentration of IL-6 in sera of NSCLC patients was higher than that of normal controls (P < 0.01) but not statistically different from that of PID patients. In patients with NSCLC, the concentration of IL-6 in serum was significantly higher than that of serum IL-6, but this difference was not statistically significant (P = 0.05). Serum IL-6 level was higher in NSCLC of advanced stages (stage IIIa, IIb and IV), as compared with that in NSCLC patients of early stages (stage Ia-IIb). BALF IL-6 level of NSCLC patients at different stages was not different. IL-6 level (in serum but not in BALF) of PID patients correlated with the serum concentration of C reactive protein (r=0.69).

Conclusion: IL-6 in BALF might be used as a marker for NSCLC. Serum IL-6 level might be an indicator for the stage of NSCLC. The serum IL-6 can also be measured by ELISA.

Magnolol can induce apoptosis in non-small cell lung cancer via caspase-independent pathway
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Magnolol is a traditional Chinese herbs drug purified from Magnolia officinalis which has multiple pharmacological properties such as antioxidant and anti-inflammatory effects. Magnolol exhibited remarkable inhibitory effects on tumor growth. However, the effect of Magnolol on non-small cell lung cancer (NSCLC) has not been clarified. In this study, the NSCLC cell lines (A549, H520, H441 and HPAEC) were treated with different concentrations (0–100 μM) of Magnolol for 24 hrs and the cytotoxic effect of Magnolol positively correlated with its concentration. Moreover, the chemotherapy drug Cisplatin at the dose of 25 μM had the same cytotoxic effect as Magnolol at 80 μM on NSCLC cell lines. Flow cytometry assay revealed that pretreatment with Magnolol at the dose of 80 μM for 24 hrs could induce apoptosis in A549 cells. We also illustrated that Magnolol-induced apoptosis in A549 cells was associated with a rapid increase in caspase-3 activity. The caspase-3 activity in A549 cells was increased by Magnolol, and the activity was associated with the decrease in the mitochondrial potential. Treatment with Magnolol induced the translocation of the Bax/Bcl-2 ratio to the mitochondrial membrane, suggesting that the Magnolol-induced apoptosis in non-small cell lung cancer cells (NSCLC cells). In conclusion, Magnolol can induce apoptosis of NSCLC cells. In addition, the apoptosis in NSCLC cells involves, most likely, caspase-independent pathway in NSCLC cells.
Methods: Plasma MP-TF activity was measured in 33 patients with LC of different stages. Blood was collected at the time of inclusion; MP were collected by ultracentrifugation, TF activity was measured with a one stage clotting assay. Informed consent was obtained from all patients.

Results: The blood of patients with stage IV LC had a higher MP-associated TF activity compared to stage III (45.56 [14.88-143.70] vs. 9.45 [3.47-16.23] arbitrary U/ml) (median [interquartile range]); p<.05 by Mann-Whitney test (fig. 1).

Conclusions: MP-associated TF activity increases in late stage LC. This observation is consistent with the hypothesis that MP-associated TF is involved in LC progression.

288. Instructive clinical aspects of lung cancer

P2803 Usefulness of serum procalcitonin in lung cancer patients with elevated serum C-reactive protein level
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Background: It is not easy to distinguish between infections and other causes with C-reactive protein (CRP) level or white blood cell (WBC) count in febrile lung cancer patients. We investigated the usefulness of serum procalcitonin (PCT) and CRP for the differential diagnosis of fever in lung cancer patients.

Methods: We measured serum PCT level and WBC count in lung cancer patients with serum CRP >0.3mg/dL. The subjects were categorized as either infection or non-infection group. Infection was verified by respiratory culture, blood culture and radiologic finding. Those who developed febrile neutropenia after chemotherapy and improved after antibiotic treatment were grouped as infection group (IG). Non-infection group (NG) comprised those who had drug fever or cancer fever.

Results: A total number of measurement was 375 samples from 285 patients. PCT showed 2.28±0.43 μg/L in IG and 0.36±0.43 μg/L in NG (mean±standard deviation p<0.001). CRP showed 17.24±8.87 mg/dL in IG and 11.6±7.93 mg/dL in NG (p<0.001). In febrile patients, there was also significant differences of PCT (1.80±0.41 μg/L in IG, 0.24±0.31 μg/L in NG, p=0.003) and CRP (17.88±8.62 mg/dL in IG, 13.11±4.96 mg/dL in NG, p=0.004) levels. Area under curve of PCT was significantly larger (0.775, 95%CI 0.690-0.861) than CRP (0.646, 95%CI 0.540-0.753, p=0.026). Sensitivity and specificity of PCT using cut off level of 0.21 μg/L was 73.8% and 59.1%.

Conclusion: Serum PCT could be more helpful for differentiation of infection from non-infectious causes of fever in lung cancer patients.

P2804 Procalcitonin: A prognosis factor in lung cancer and a marker for small-cell lung cancer
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Introduction: Serum procalcitonin (PCT) is used for the early diagnosis of bacterial infections. PCT is also a prognostic factor in thyroid carcinomas and PCT level is also usually increased in small cell lung cancer.

Aim: To evaluate the serum PCT level as a diagnostic and prognostic marker of lung cancer.

Methods: Sera sampled between December 2008 and November 2010 for neuron-specific enolase (NSE) dosage at the Rouen University Hospital were retrieved. A PCT dosage was performed on samples from untreated patients with histologically proven lung cancer.

Results: From the 147 blood samples selected, 66 came from adenocarcinoma patients, 58 from neuroendocrine lung cancers (NELC) including 31 small cell lung cancers, 6 large cell lung cancers and one atypical carcinoid, 23 from squamous cell carcinomas and 2 sarcomas.

Conclusion: Serum PCT should not be used for the early diagnosis of bacterial infection in patients with a NELC. Elevated PCT appears to be a marker of poor prognosis in lung cancer patients.

P2805 Serum levels of interleukin 8 and plasma levels of osteopontin in patients with non-small cell lung cancer during chemotherapy
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Interleukin 8 (IL-8) and osteopontin (OPN) are multifunctional cytokines associated among other with tumor progression and metastasis. The aim of the study was to evaluate serum levels of IL-8 and plasma levels of OPN in patients with NSCLC undergoing chemotherapy. Peripheral blood samples were taken before and after four cycles of chemotherapy (DDP+VP) and in the case of progression of disease. The study included 29 patients diagnosed histologically with lung cancer (stage IIB 12 patients, stage IV 17 patients). IL-8 and OPN levels were determined by ELISA (R&D). Mean levels of IL-8 and OPN significantly increased with progression of the malignancy: serum IL-8 levels in stage IIB and IV were 19.82±9mg/ml and 46.38±9mg/ml respectively, (p<0.001), plasma OPN levels in stage IIB and IV were 50.3±4mg/ml and 73.0±2mg/ml respectively, (p<0.02). Cytoreduction treatment had no influence on the levels of IL-8 and OPN in comparison with their mean levels before treatment (in both stages). The progression of disease resulted in significant increase of mean serum level of IL-8 (34.31±3.38 pg/ml) when compared to mean initial (before treatment) serum level of IL-8 (23.78±2.17pg/ml) (p<0.05). Mean plasma level of OPN were elevated but without statistical significance. In conclusion, chemotherapy had no influence on the serum IL-8 levels and plasma OPN levels. The increased IL-8 and OPN levels possibly relate to the activity of lung cancer.

P2806 Role of C reactive protein in non small cell lung cancer staging
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Hypothesis: Advanced stage in lung cancer is associated to increased CRP levels in serum.

Objective: To compare blood levels of different inflammatory markers (TNFα, IL-8, C Reactive Protein [CRP] in patients with different stages of lung cancer.

Method: 56 patients diagnosed of lung cancer were included (53 males, 64.59±9.73 years, X±SD). All of them underwent studies for disease staging, including fiberobronchoscopy and computed tomography, and positron emission to-
The search for prognostic and predictive biomarkers in NSCLC is studied in relation to overall survival. However, a majority of all patients lack genetic disease in non small cell lung cancer.

Aim: To study the prognostic potential of haemoglobin (Hgb), platelet (Plt) - and white blood cell (WBC) levels at time of diagnosis in non-small cell lung cancer (NSCLC) patients.

Background: The search for prognostic and predictive biomarkers in NSCLC is intense. With an increasing number of targeted agents available the present focus is on the genetics of the tumour. However, a majority of all patients lack genetic markers that favour targeted therapies. Thus the need for basic prognostic factors to optimise the treatment for each individual case is expected to increase in the future.

Methods: 833 NSCLC patients, stage I-IV were included in the study. WBC, Plt, Hgb, gender, age at diagnosis, stage, surgery and first-line chemotherapy were studied in relation to survival.

Results: For patients with Hgb <110g/L and Hgb >110g/L the median survival was 11.2 and 14.5 months respectively (p<0.0001). For WBC >9,0×10⁹/L and <9,0×10⁹/L the median survival was 11.6 and 15.4 months respectively (p<0.0001). For Plt >350×10⁹/L and <350×10⁹/L the median survival was 11.2 and 14.9 months respectively (p<0.0001). For patients with no pathology in the studied markers compared to those with pathological results in all three markers the median survival was 16.0 and 8.0 months respectively (p<0.0001).

Conclusions: The level of the three studied biomarkers corresponds significantly to outcome. A trend for worsened prognosis is shown when combinations of two pathological markers are present. With all three biomarkers pathological the median survival is halved compared to the group with normal levels. The results are important for the decisions regarding treatment choice and intensity.

Analysis of the clinical feature of 833 patients with lung cancer

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Objective: To investigate the clinical feature of lung cancer.

Methods: We retrospectively analyzed the clinical data of inpatients diagnosed with primary bronchochegic carcinoma who registered in our hospital between 2007 and 2008.

Results: The age of onset of lung cancer was 59 years old. 50.1% of the patients had a history of smoking. 93.8% of whom were males. Coughing, expectoration, emaciation, weight loss, chest pain, dyspnea and pyrexia were the most common symptoms. The levels of NSE and CYFRA21-1 in males were higher than those in females, and the levels of serum CYFRA21-1 in senile were higher than those in non-senile. The levels of serum NSE and CYFRA21-1 in smokers were higher than those in non-smokers, while they were higher in patients with central type lung cancer than those in patients with peripheral type lung cancer. The levels of serum NSE in small cell lung cancer patients were higher than those in non-small cell lung cancer patients. The levels of CEA in patients with adenocarcinoma were higher than those in patients with squamous cell carcinoma, while the levels of serum CYFRA21-1 were higher in the latter. The more advanced the disease was, the higher the levels of serum CEA, NSE and CYFRA21-1 were. Carcinoma was the most commonly seen in the upper lobes of both sides of the lungs. 66.8% of lung cancer belonged to peripheral type. Adenocarcinoma and squamous cell carcinoma were the most common pathological type. 66.0% of lung cancer patients were in advanced stage when diagnosed, and 55.2% had metastasis to mediastinal lymph nodes. Bones were the most common sites of metastasis.

Conclusions: The combined detection of serum CEA, NSE and CYFRA21-1 could help to identify some of lung cancer.
Conclusions: Neoadjuvant therapy increased the perioperative complications in this group of patients compared with a similar group undergoing anatomical lung resection in the same institution. The most common complication in patients receiving induction chemotherapy was detected at the group with neoadjuvant therapy. Strategies to prevent these complications will be important, especially if chemotherapy before resection becomes the standard for all patients with non-small cell lung cancer.

P2812 Patterns of recurrence after resection surgery of lung cancer: Clinical correlations and survival

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Objectives: Analyze the patterns of recurrence and survival in lung cancer patients under surgery

Methods and results: Observational, retrospective cohort of lung cancer patients undergoing surgery during years 1999-2006 in CHOU-Spain. We performed a descriptive analysis of data, the continuous variables to be non-Gaussian are shown as median and categorical variables as frequencies and percentages. We determined the clinical factors associated with recurrence and survival by Kaplan-Meier curves and Cox regressions models. We used SPSS 15.0 software

Results: 168 patients underwent surgery, of whom 79.8% were men, and the median age was 67 years (35-82). 74 ex-smokers (44%) and 63 active smokers (37.5%). Most common histological type was epidermoid 88 (52.4%) followed by adenocarcinoma 48 (28.6%). The median tumor size in CM was 3.3 (0.9), and most common site of differentiation in 77 (45.8%). The pathological stages were: 91 (57.6%), II 26 (16.5%), IIIA 30 (19%), IIIB 11 (6.5%). The most frequent surgical resection was lobectomy. Recurrence occurred in 78 (46.5%) patients, related with tumor size (p = 0.002) and pathological stage (p = 0.001), no differences in the histological subtype (p = 0.232). Coughing and CNS disorders were the most prevalent symptoms of recurrence and extrathoracic involvement was in 42 cases (58.3%). The median survival in those who had recurrence was 9 months, with 95% CI [5.129 to 12.871]. Other risk factors of death were tumor size (p = 0.002) and pathological stage (p < 0.001)

Conclusions: Most patients do not relapse. Recurrence was more frequent extrathoracic location. The tumor size and advanced stages determine higher risk of recurrence and mortality.

P2813 Radiofrequency ablation in the treatment of malignant lung tumors

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Objectives: Radiofrequency ablation (RFA) has gained acceptance for thoracic surgery use but few data exist regarding its value in thoracic oncology. The aim of this study was to report our experience RFA for malignant lung tumors

Methods: From 2010 27 patients were underwent RFA for peripheral malignant tumors: metastases in 20, primary lung cancer in 7. Range of threes dimensions were from 7 to 52 mm (mean 27 mm). Renal cell carcinoma metastases had 4 patients, metastases of colorectal cancer - 10, metastases of lung cancer - 5 and hepatocellular carcinoma - 1. Indications for RFA: inability undergo thoracotomy (9), as alternative complication pneumonectomy after lung resections (4), necessity to save lung tissue for patients with multiple lung metastases (14). We used transcortaneous RFA in 7 cases. In 14 cases thoracoscopic detection of tumor node before RFA was used. In 6 cases RFA used during thoracotomy. Used needle electrode with test portion 30 mm, maximal power and exposition of 10 min. Mediania follow-up was 19 months (2-32).

Results: No postoperative mortality. Post-operative complications were associated with pulmonary tissue inflammation (6 cases). Average hospital stay of uncomplicated patients was 3-7 days. At present no local recurrences were diagnosed. But 7 patients developed new pulmonary and hepatic metastases from 3 to 18 months after RFA and 9 patients died from progression of oncological diseases from 6 to 26 months after RFA. Four patients have died from comorbid diseases from 1.5 and to 5 months after RFA. The median survival was 19.5 month (1.5-30).

Conclusion: RFA is a reasonable option if a lesion is unresectable or necessity tissue sparing for multiple lung resection.

P2814 Second primary lung cancers developed following different system tumors

Cigdem Ozdilekcan1, Sevim Turanlı2, Necia Songur3, Huseyin Cakmak4

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Aims and background: This study aimed to investigate clinical characteristics and prognosis of secondarily developed lung tumors in the cases having different system malignancy and to evaluate the relationship with the primary tumor.

Methods: Thirty patients diagnosed as second primary lung cancer those admitted to have been included in the study.

Results: The patients were grouped: synchronous group (n=7, 16.7%) and metachronous group (n=2, 83.3%). The age of primary malignancy and second primary lung malignancy was median 59.5 (range, 38-82 years), and 63 years (range, 39-83 years) respectively. The rate of quitting smoking among all patients before the diagnosis of lung cancer was 50%, current smoker rate was 30%. Second cancer was detected in 50% of the patients within the first 5 years. The most frequent primary localization was larynx (40%). Majority of patients received surgical treatment for primary localized carcinoma, while for secondarily developed carcinoma, the most frequent treatment choice was chemotherapy and/or best supportive care. There was no statistical relationship between the response to treatment of first cancer and the duration of cancer developed secondarily (p=0.36). The overall survival of groups was found 24 months (95% confidence interval: 18.30 months) and 12 months (95% confidence interval: 10-14 months) respectively for synchronous and metachronous groups.

Conclusions: Close follow-up on pulmonary system especially within the first 2.5 years after primary disease and encouragement on quitting smoking is important.
Background: Erlotinib is a tyrosine kinase inhibitor (TKI) approved for 2nd or 3rd line treatment of advanced NSCLC.

Aim: Evaluate the smoking impact on objective response (OR) and survival of pts treated with erlotinib.

Method: Retrospective analysis of OR, overall and post-erlotinib (PE) survival in pts treated with this TKI from 2006 til December 2010, taking into account the gender, smoking status, histology and epidermal growth factor receptor (EGFR) gene mutational status.

Results: Over the past 5 years, 104 pts (57 males) began treatment with erlotinib: 66 adenocarcinomas (AC), 18 squamous cell carcinomas (SCC) and 20 NSCLC. Smoking status: 48 non-smokers (NS); 31 ex-smokers (ES) and 25 active smokers (AS). Median overall survival of 23 months (m). There was no significant difference in overall survival among pts of different gender, staging or smoking status. Median PE survival of 6 m. The PE survival was higher in NS (12 vs 6 m in ES and 4 m in AS: p=0.077), AC (10 vs 5 m in SCC and 3 m in NSCLC: p=0.013) and in mutated pts (14 vs 6 m in non-mutated: p=0.003). Analyzing by histologic subtypes, in AC survival remains higher in NS (21 vs 10 m in ES and 2 m in AS: p=0.021). Analyzing by mutational status, smoking habits lose significance. Assessing the OR to erlotinib, 50 pts had disease progression and 48 disease control (DC). DC analyzing by mutational status, smoking habits lose significance. Assessing the PE survival among pts with a presence or absence cardiovascular comorbidities. There was not a statistically significant relationship between shorter survival time and a history of cardiovascular comorbidity (p=0.104).

Conclusions: This study did not show a statistically significant effect of the presence of cardiovascular comorbidity on survival of patients in the first and second stage of the disease.

Background: Bronchopulmonary carcinoids (BPCs) are rare neuroendocrine tumors. Metastatic BPC (M-BPC) represents less than 10% of all BPCs.

Aim: A retrospective study of a 5 years’ consecutive series of M-BPC patients, treated in a tertiary referral center.

Methods: Demographics, symptoms, staging, pathology, therapy and survival were compared for non-metastatic (NM-) and M-BPC.

Results: Of 57 BPC patients, 12 (21%) had metastases. Five were truly metastatic at diagnosis. No differences were observed for age, smoking status and gender. Hemoptysis was mostly found in M-BPC (4/12); infection and absence of symptoms in NM-BPC (both 6/45). Somatostatin receptor imaging was performed in respectively 20% and 92%, FDG PET in 67% and 75%, Ki-67 staining in 24% and 75%, chromogranin A staining in 64% and 83% of NM- and M-BPC patients. M-BPC was predominantly treated with chemotherapy (42%) and somatostatin analogues (58%), NM-BPC with surgery (91%). Median survival was 52 months for M-BPC, while not yet reached for NM-BPC patients (p=0.01).

Conclusions: In our center, a larger proportion of M-BPC patients was treated compared to literature. Major differences between NM-BPC and M-BPC were observed for treatment choices. Survival was significantly worse for M-BPC, although much better compared to more common lung cancer types.

Background: The treatment of patients with locally advanced non-small-cell lung cancer is controversial. Surgery remains the gold standard treatment even in patients initially judged inoperable.

Methods: From January 2009 to May 2010, neoadjuvant chemotherapy was indicated in 27 patients with NSCLC (25 men, 2 women). The mean age was 65 years. The different stages were: IIB, 5; IIIA, 17 (with 6 of whom in stage IIIB); IIIB 2 and IV, 3.

Results: Twenty-three patients received neoadjuvant chemotherapy, 2 refused the induction treatment and 2 had impaired their status. The neoadjuvant chemotherapy regimen was gemcitabine-cisplatin in 17 patients and vinorelbine-cisplatin in 6. Only 5 patients underwent complete surgical treatment after induction: stage IIIB, 1; IIIB, 1; IIIA, 1 and IV, 2 (operated adrenal metastasis in one patient and operated adrenal metastasis in one patient). Surgical treatment was not achieved after neoadjuvant chemotherapy in 18 patients because of progressive disease.

Conclusion: Neoadjuvant chemotherapy offers several potential benefits. But, it may delay surgery or eliminate eligibility as a surgical candidate. A patient’s rigorous selection for this type of multimodal treatment is essential.

Introduction: Comorbid conditions may affect survival by influencing treatment decisions and prognosis.

Aim of this study was to determine the impact of cardiovascular comorbidity on the survival of patients in the first and second stage of NSCLC.

Methods: The study included 140 patients with NSCLC, in the first and second stage who were treated in the period from January 2004 December 2006. 60 patients (30 in the first and 30 in the second stage) were treated surgically, and 80 patients (30 in the first and 40 in the second stage) is due to the presence of cardiovascular comorbidity treated with chemotherapy and/or radiotherapy and these patients received standard chemotherapy with cisplatin (60mg/m2, 1st day) and etoposide (100mg/m2, 1-3. day), and radiotherapy (40 Gy).

Results: In 43 patients (30.71%) was established cardiovascular comorbidity. The most frequent comorbidities were chronic hypertension (22 or 15.71%), ischemic heart disease (19 or 13.57%) and hypertension (19 or 13.57%). Cardiovascular comorbidities were higher in smokers (p=0.019) and patients with low Karnofsky status (p=0.001).

Median survival for all patients was 19.82 months (in the first stage 20.33, and in the second stage 19.31). Kaplan-Meier survival curves were used to compare survival time among patients with a presence or absence cardiovascular comorbidities. There was not a statistically significant relationship between shorter survival time and a history of cardiovascular comorbidity (p=0.104).

Conclusions: This study did not show a statistically significant effect of the presence of cardiovascular comorbidity on survival of patients in the first and second stage of the disease.
Case description: A 55-year-old previously healthy male presented with complaints of bilateral chest wall pain for the last 4 weeks. Patient denied any history of cough, fever, dyspnea, hoarseness, or any rash. He had smoked a half pack per day for about 30 years. Physical examination was normal as were laboratory studies. Chest CT scan demonstrated a 2.5 cm mass adjacent to the left diaphragm with small satellite nodules. Open lung biopsy did not yield any definite diagnosis. Further workup with MRI of spine, CSF analysis and a para-neoplastic antibody panel were negative. A nerve conduction study demonstrated an axonal polyradiculoneuropathy. Almost a year later a repeat chest and abdominal CT scan showed innumerable bilateral lung nodules and masses. It also showed peculiar motting of the kidneys. A repeat thoracotomy and lung biopsy showed findings consistent with pulmonary lymphomatoid granulomatosis (EBV positive diffuse large B-cell lymphoma of the lungs).

Discussion: Pulmonary lymphomatoid granulomatosis is an uncommon multi-organ systemic disease with predilection to lungs and characterized by multiple pulmonary nodular lesions with lymphocytic invasion of vascular walls on biopsy. The skin, kidney, and neurologic system may be affected concurrently or independently. Cough and dyspnea are the most common presenting symptoms in patients with lung involvement. Physical examination and laboratory studies are generally non-diagnostic. Chest radiography typically reveals multiple poorly defined nodules and/or masses in the mid- and lower-lung zones; diffuse reticular abnormalities may also be present. Therapy ranges from observation to treatment with prednisone or chemotherapy.

**289. Pleural and mediastinal malignancies: management and rare clinical cases**

P2825

**Medical pleurodesis – Safety, effectiveness and adherence to the guidelines: East of England DGH experience**

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The aim of the study was to review the safety and effectiveness of medical pleurodesis performed in our trust. This study was done in The Queen Elizabeth Hospital, Kings Lynn, United Kingdom. We looked at the medical pleurodesis performed from April 2008 to May 2010. The results were assessed against the British Thoracic Society guidelines for medical pleurodesis. We also looked at the side effects and success rate of the procedure.

Forty three events were analysed in 41 patients. Forty four patients were admitted in 2008, 18 patients in 2009 and 7 patients in 2010. Twenty seven (64%) were lung cancer patients in the NELCN who are present late with advanced disease, only 41% of these patients came through a respiratory specialist as a first port of call, and only 35% as urgent cancer referrals. Chemotherapy was offered to 74% of these patients, but only 50% had it. Most of those did not have chemotherapy because of poor performance status. However in two cases chemotherapy was delayed in order to wait for symptoms. The current BTS 2007 guidelines evidence that chemotherapy before symptom progression has a better outcome.

Port site radiotherapy was given to a third of patients, those who did not have chemotherapy. This is in line with the BTS 2007 statement. The NELCN has a high case load of mesothelioma. Diagnoses are moving uniformly across the network towards early CT biopsy or VATs biopsy. Palliative surgical pleurodesis is common and chemotherapy is being offered to three quarters of patients. Mesothelioma MDT’s are operational and assist in optimizing patient pathways.

P2824

**Pleural and mediastinal malignancies: management and rare clinical cases**

Fibrosing mediastinitis mimicking bronchogenic carcinoma

Deniz Keskul,1 Hulya Bayiz1, Nesilhan Mulutlu4, Adem Keyuncu1,2, Funda Demirag1,2, Gulidan Dagil1, Bahadir Berkas1, Mine Berkoglu1,2,2nd Chest Diseases Clinic, Ataturk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey; 1Pathology Clinic, Ataturk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey; 3Chest Surgery Clinic, Ataturk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey

We present a patient with fibrosing mediastinitis mimicking bronchogenic carci-

oma. A 32-year-old male patient admitted with cough and hemoptysis. There was no history of tuberculosis, prior respiratory disease. He had a diagnosis of hepatosteatosis and diabetes mellitus for two years. He had a smoking history of 8 pack-years. Vital signs, physical examination were normal. Apart from a high Glu:177 mg/dL, ESR:48 mm/hr, rutine laboratory analysis were normal. The chest radiograph revealed prominence of right hilum. Thorax CT revealed 4cm mass lesion in the right hilum and multiple mediastinal, right hilar conglomerated lymph nodes.

In PET-CT SUVmax of the hilar lesion was 9.74. Fibroptic bronchoscopy showed mucosal distortion of right upper lobe. Mucosal biopsy was unremarkable. FIBUS-TBNA biopsy revealed CD-45 positive normal lymphoid cells. Cervical mediastinoscopy was undiagnostic. Diagnostic thoracotomy confirmed the diagnosis of fibrosing mediastinitis. Hilar mass was a conglomerated lymph node showing dense hyalineised fibrous tissue with chronic inflammation. In the etiology we thought that fibrosing mediastinitis results from a prior tuberculosis infection, since our country is endemic for tuberculosis. There is no proven effective medical therapy for fibrosing mediastinitis. Despite the fact we initiated both antitubercu-
losis and systemic corticosteroid therapy after informing the patient. The patient is stable after two months of therapy.

P2822

**A 55 year old man with bilateral pulmonary nodules, neuroopathy and renal nodules**

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Mesothelioma in north east London

P2823

**Fibrosing mediastinitis mimicking bronchogenic carcinoma**

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losis and systemic corticosteroid therapy after informing the patient. The patient is stable after two months of therapy.
normal apart from a high erythrocyte sedimentation rate (120 mm/hr), anemia (hb: 10.9 g/dl) and hypoxemia (PaO2: 48 mmHg). Computed tomography revealed multiple mediastinal lymph nodes, bilateral pleural thickenings, paramediastinal mass lesion in the left lower lobe and multiple pulmonary nodules.

Cranial CT was normal. Abdominal USG revealed liver metastasis with multiple hyperechoic nodules 2 cm in diameter. Transbronchial biopsy via fiberoptic bronchoscopy revealed the diagnosis of malignant mesothelioma infiltration. The tumor was diffusely positive for calretinin and focal positive for keratin 5.6. The patient died one week after diagnosis.

P2827
Benefit of the serum-effusion albumin gradient in congestive heart failure patients
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Objective: To compare between light’s criteria and serum-effusion (S-E)albumin gradient in assessment of transudate effusion in CHF patients.

Material and method: Eighty-six patients who had pleural effusion and suspected CHF were enrolled in this study between October 2008-September 2010. Suspected CHF was defined by clinical or echocardiography. Inform consents were done in all volunteers. Exclusion criteria was previous thoracotomy or coronary by pass graft 3 month before study. Thoracocentesis was done to evaluate transudate effusion by light’s criteria and S-E albumin gradient > 1.2 mg/dl. Definite diagnosis of pure CHF was no effusion after treatment with diuretics and pleural ProBNP > 4000 ng/dl. Combination of pleural disease and CHF were defined by confirmed pleural disease with pleural biopsy and/or VAT, partial response with diuresis and high pleural ProBNP

Result: 12 (13.95%), 56 (65.11%), 17 (19.76%) of all were pure pleural disease, pure CHF, combination of pleural disease and CHF. Sensitivity/specificity/accuracy of S-E albumin gradient and light’s criteria and in diagnosis of CHF (both pure and combined) were 90.133.300.2%, 64.780.067.4%. No correlation between amount of diuretic drug and “exudate” criteria from lights (p=0.66).25 (27.2%) patients were previous post thoracotomy or coronary bypass graft. 7 of 25 patients had loculated effusion. There was correlation between previous surgery with loculated effusion and effusion from combination of pleural disease and CHF (p=0.22).

Conclusion: There is benefit use to S-E albumin gradient > 1.2 mg/dl to diagnose CHF patients who suspected CHF with or without pleural disease. No correlation between diuresis and exudate from Light’s criteria.

P2828
Epigenetic deregulated translation control of C/EBP-alpha leads to increased mesothelioma cell proliferation
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Malignant pleural mesothelioma (MM) resists all available anticancer therapies. A major pathology of MM is the uncontrolled cell proliferation and the fast local spreading with rare metastasis. Therefore the inhibition of proliferation is a major therapeutic target. Proliferation of MM cells was linked to mitogen activated protein kinase (MAPK) activity. In this study we characterised the regulation of MAPK regulated CCAAT/Enhancer binding proteins (C/EBP) and their role in MM cell proliferation. In 5 human MM cell lines, cytosolic and nuclear protein expression was determined by western blot, or C/EBP-β, -γ and -α MAPK together up-regulated the expression of C/EBP-α, while C/EBP-β was not expressed. Compared to mesothelial cells C/EBP-α translation was reduced in MM, while the mRNA was constitutively expressed. MM cells expressed a high level of the C/EBP-α transcription suppressor calreticulin, while eIF4E was not significantly modified. Cell proliferation was inhibited by either the blockade of Erk1/2 or p38-β and -γ MAPK, or C/EBP-β. Translation with a C/EBP-α expression vector reduced proliferation and increased the MM cell’s sensitivity to steroids. Our data implies that in human MM cells an epigenetic mechanism deregulates the translation control of the cell differentiation factor C/EBP-α which leads to increased proliferation and drug resistance.

P2829
Granulomatous reaction – A common cause of mediastinal and hilar lymphadenopathy in non-pulmonary malignancies
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Introduction: Patients with non-pulmonary malignancies are followed with CT for exclusion of metastatic disease. Enlarged mediastinal or hilar lymph nodes can be signs of metastases.

Aim: We report the outcome of 45 consecutive patients referred for EBUS-TBNA due to mediastinal or hilar lymph nodes detected on CT at clinical follow-up for non-pulmonary malignancies.

Material and methods: EBUS-TBNA was performed 17 (0.5-116) months (median range with range) following the primary diagnosis: 28 patients had epithelial malignancies, 6 melanomas, 6 lymphomas, 4 germinal cell carcinomas, and 1 patient sarcoma.

Results: In 45 patients, 90 mediastinal and hilar lymph nodes were punctured. In 6 lymph nodes no lymphocytes were detected (93.3% representative samples). Granulomatous reaction was found in 19 patients (42%), and in another 12 (27%), the lymph nodes were normal. In one patient, no lymphocytes and no malignant cells were present, and 24 months follow-up was uneventful. Metastases were seen in only 12 patients (27%), and in one patient a malignancy other than the primary tumor was detected. In 13 patients with colon cancer, the largest subgroup, metastases were found in 3.

Conclusions: Cytopathological investigation of enlarged mediastinal or hilar lymph nodes in non-pulmonary malignancies is required to confirm the diagnosis, as the majority seem to be benign.

P2830
Patients with malignant pleural effusions who are treated with indwelling pleural catheters spend fewer days in hospital
Edward Fish1,2, A. William Misk1, Y.C. Gary Lee1,2. 1 Pleural Diseases Unit, Sir Charles Gardiner Hospital, Perth, Western Australia, Australia; 2School of Medicine, University of Western Australia, Perth, WA, Australia

Introduction: Malignant pleural effusions (MPE) are common and reducing hospitalization is a key management goal for these patients. Treatment strategies are changing with the advent of indwelling pleural catheters (IPC), a new ambulatory treatment for patients with MPE. We hypothesized that those patients managed with IPC spend fewer days in hospital compared with pleurodesis.

Methods: A prospective, non-randomized study involving all major respiratory centers in Western Australia. Patients diagnosed to have MPE were prospectively followed up until death or to the end of the one year study. In the absence of accepted guidelines for IPC-use, the choice of treatments (pleurodesis, IPC or repeated thoracocentesis) was made by the treating clinicians. Hospital admissions were analysed on an intention to treat basis from the time of the first procedure.

Results: 160 patients with MPE were recruited. 31 patients were managed with talc pleurodesis, and 34 received an IPC. The remaining patients only required simple thoracocentesis, either because of poor prognosis, lack of effusion recurrence, or lack of symptom relief with initial drainage. Total hospital admission days were significantly lower in patients treated with IPC (median, 25.75th percentiles) at 6-5 days (3.75-13.0) compared with pleurodesis at 18.8 (8.0-26.0), p<0.002 (Mann-Whitney ranked sum test). Effusion-related admissions were even more significantly reduced at 3.0 days (1.75-8.25) against 10 (6.0-18.0), p<0.001.

Conclusion: Patients with MPE who are treated with an IPC spend fewer days in hospital compared with pleurodesis.

P2831
The burden of mesothelioma mortality: Estimation as the first step to prevention
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Background: Mesothelioma is a rare cancer that principally affects the pleura and is almost always caused by asbestos exposure. Mesothelioma incidence has increased in South East England of which East Kent is a major part, particularly for men aged over 70 years, reflecting areas of asbestos use in shipbuilding and industry in the past.

Methods: The aim of the study is to estimate the current burden of cancer in the area of East Kent in the UK attributable to occupational factors, and identify carcinogenic agents, industries and occupations for targeting risk prevention.

Data of all cases diagnosed at East Kent Hospitals NHS Trust were collected retrospectively from April 2009 to March 2010.

Results: There were a total of 15 cases in East Kent Hospital NHS trust, UK over the period of one year which is a significantly high number as compared to previous years, the current population being 614,576. All of them were male. Median age was 74 years and median survival from diagnosis was 8.9 months. 85% had documented evidence of definite or probable exposure to asbestos. There
were 7 cases that were treated with chemotherapy, 6 patients had radiotherapy and 2 patients with advanced malignancy had palliative treatment. No patient had radical surgery and there was minimal difference in relative survival between men with localised and non-localised disease.

Conclusion: In Great Britain, where asbestos use continued later than many other countries, the peak is anticipated to occur later between 2011 and 2115. Cancer networks, especially those with primary care trusts with high incidence, need to be aware of this disease and ensure that risk reduction strategies and services are in place to assist these patients.

P2832
Evaluation of pulmonary reexpansion after thoracocentesis using electrical impedance tomography
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Introduction: The time to maximum lung reexpansion after a thoracocentesis (Thc) is unknown. This limitation is due to the lack of a method to accurately and continuously gauge the lung reexpansion. Electrical impedance tomography (EIT) is a method able to accurately measure relative alterations in lung ventilation and may be an attractive method to evaluate lung function affected by a pleural effusion and the effect of Thc.

Objectives: Quantify the time to maximum lung expansion.

Methods: EIT electrodes were placed around the thorax two centimeters above the effusion lower level. The EIT images were recorded before, immediately and at 15 min intervals after Thc until three consecutive measurements without alteration in the ventilation of affected lung (defined as a ventilation variation <10%).

Results: We evaluated seven patients with pleural effusion. The mean withdrew effusion volume was 1440 mL. Five patients reexpanded the lung. Before Thc, their mean lung ventilation proportion of the affected lung over the unaffected was 0.19 and rose to 0.71. Two patients achieved maximum reexpansion immediately after Thc, one after 15, one after 30 and one after 60 min. Two patients did not reexpand their lungs.

Conclusions: Patients that reexpand their lungs after thoracocentesis achieve maximum lung reexpansion immediately or in less than 60 minutes.

P2833
Malignant pleural mesothelioma: Facts & survival rate
Catarina Guimarães, Lígia Fernandes, Luís Rodrigues, Ana Figueiredo, Fernando Barata. Pulmonology Department, Centro Hospitalar de Coimbra-EPE, Coimbra, Portugal

Background: Malignant pleural mesothelioma is the most common type of malignant mesothelioma. Classically described as rare neoplasms, malignant pleural mesothelioma is considered an almost incurable tumour with increasing incidence worldwide, mainly as a result of previous exposure to asbestos – its chief risk factor.

Objectives: Characterize patients with pleural mesotheliomas, determine the time to progression and establish median survival rate.

Materials and methods: A retrospective analysis of all cases of pleural mesotheliomas diagnosed in our Department of Pulmonology, between the years of 2000 and 2009.

Results: Pleural mesotheliomas were diagnosed in 25 patients, 4 females and 22 males. Their age average was 62 years (minimum 40; maximum 76). The majority, 53%, had a history of tobacco exposure (28% were ex-smokers while 25% were current smokers). In 44% of all cases, there was recognized exposure to asbestos fibbers in the past. Twenty one patients presented the epithelial type of mesothelioma and only four had the mixed type. Their therapeutic approach included chemotherapy and in 21 patients local adjuvant radiotherapy was used. The time to progression was 7 months, median survival 11 months and one-year survival rate of 44%.

Conclusion: The incidence of pleural mesotheliomas was much higher in males than in females. Previous exposure to tobacco and asbestos fibbers was significant. Pleural mesotheliomas have a dismal prognosis, with a high mortality rate and low median survival time.

P2834
Acute pleural service: Experience and pathways
Burhan Khan, Marika Townsend. Department of Respiratory Medicine, Darent Valley Hospital, Dartford, Kent, United Kingdom

Introduction: Pleural effusions are common and may be the first sign of malignancy or can develop in patients with a confirmed malignancy. It generally indicates advanced disease, forbears deterioration in performance status, increased symptom load, and limited life expectancy. However, not all of these patients necessarily need hospitalisation or a chest drain.

Aims: To ascertain the qualitative and quantitative benefits of providing an acute pleural service.

Results: From July 2010 to date 25 patients were referred to the Acute Pleural Service. The types of pleural pathologies and pathway are shown below.

Aetiology of pleural disease of patients in Acute Pleural Service

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>18</td>
</tr>
<tr>
<td>Transudate</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
</tr>
</tbody>
</table>

Conclusion: Patients with either known malignant pleural effusion and those on first presentation may be managed as elective day admissions in an Acute Pleural Service pathway delivered by a Chest Physician with competency in thoracic ultrasound. This enables rapid assessment for prompt diagnosis, relief of symptoms and onward referral for VATS, medical thoracoscopy, PleurX, chest tube pleurodesis, or repeated pleural drainages as appropriate. This also represents another modality in managing patients with recurrent pleural effusion accumulation, and avoids unnecessary admission & hospitalisation to an acute hospital.
P2335
First ever report of histologically proven bronchiolitis obliterans organizing pneumonia after antineoplastic treatment of a malignant pleural mesothelioma with cisplatin and pemetrexed
Markus Lehrmann, Axel Tobias Kempa, Franz Stanzel, Monika Serke. Langenklinik Hemer, Pneumologie, Hemer, Germany

We report a case of a 74 year old patient diagnosed with malignant pleural mesothelioma who developed an interstitial pneumonia following chemotherapy with platinum and pemetrexed.

The patient was treated with 6 courses of chemotherapy. On admission for the sixth course he reported dyspnea on exertion. Blood gas analysis showed mild hypoxemia. Computed tomography of the chest showed patchy opacities in both lungs, some with a ground glass pattern. Six weeks later and after being treated with several antibiotic agents, the respiratory failure and radiological findings had dramatically worsened. We performed a transbronchial lung biopsy. The histopathological examination of the biopsies showed the pattern of bronchiolitis obliterans and organizing pneumonia. The patient was treated with steroids for several weeks. While radiologic findings clearly improved, the respiratory failure even worsened. The patient remained severely impaired in his quality of life.

Despite up to 20 percent of patients treated with an antineoplastic agent are estimated to have some form of lung toxicity, just one suspected case of interstitial pneumonia after chemotherapy with pemetrexed has been reported. Though, the diagnosis has not been proven historically [1]. Especially as the antifolate agents gemcitabine and methotrexate are well known to cause lung injury, we think that pemetrexed must be considered as the causing agent of the lung injury in our patient.


P2336
An analysis of indwelling pleural catheter (IPC) insertions for malignant pleural effusions
Elaine Reid, Pasupathy Sivasothy, Stefan Marciniak. Respiratory Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Introduction: Persistent malignant pleural effusion (MPE) is a common complication of malignant disease. IPCs are a safe effective strategy to relieve dyspnoea, maintain quality of life, reduce hospitalisation and length of hospital stay.

Objective: To describe the use and outcomes of IPCs in management of MPE.


Results: 47 IPC insertions for MPE were performed in 44 patients (1 bilateral and 2 retrosternal cases).

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>69</th>
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</table>

21 patients had IPC insertion due to trapped lung, 19 patients after failed pleurodesis. Median hospitalisation 2 days for elective admission (IQR 1), 6 days for emergency admission (IQR 2.5). Median survival post insertion, if still in situ at time of death, 35 days (IQR 28), mean 54 days (SD 54.5). Complication rates were 4% for catheter related sepsis, 2 cases of cellulitis, 2 cases of skin sensitivity to dressing, 1 tube displacement and 1 fracturing of IPC requiring removal. IPCs were removed in 4 patients after time of death, 35 days (IQR 28); mean 54 days (SD 54.5). Complication rates were 3% for catheter related sepsis, 1 case of cellulitis and 1 fracturing of IPC requiring removal.

Conclusion: IPC’s are effective and safe for management of MPE with low complication rates and obvious cost benefit advantage in reduced hospital admissions offering immediate and sustained relief of symptoms.

P2337
Unusual case of multiple pleural masses
Vena Srpa, Parthipan Kanthapillai. Respiratory Medicine, Laton & Dunstable Hospital, Laton, United Kingdom

A 80 year old lady was referred for evaluation of multiple pleural shadows. She was diagnosed to have myasthenia gravis 30 years ago and was treated with azathioprine until now. Six years ago she underwent bone marrow biopsy for investigation of anaemia which revealed hypoplastic marrow with specific red cell aplasia including features consistent with azathioprine treatment.

Her hemoglobin was 11.5g/dl. CT scan of the chest revealed multiple pleural masses. CT guided biopsy of the pleura showed bone marrow with apparently normal granulocytes, normoblasts, megakaryocytes and other myeloid elements. There was no evidence of leukemia or malignancy noted. There was no pleural or pulmonary tissue identified in the biopsy and the features were consistent with extra medullary hemopoiesis (EMH).

EMH is the proliferation of blood elements outside the bone marrow cavity. This mainly involves reticuloendothelial system (liver, spleen & lymph nodes) but is also known to occur in every organ of the body including thyroid, pericardium, kidney and lungs. Only a few cases of intra thoracic EMH have been reported in literature.

These may manifest as paraoesophagus masses, pleural masses or haemorrhaxas either alone or in combination. They occur characteristically either unilaterally or bilaterally in the posterior mediastinum. They present as rounded soft tissue opacities peripherally with a clear cut outline. Neither calcification nor bony erosion has been reported in these masses. EMH thus forms one of the important differential diagnoses of posterior mediastinal masses. This case illustrates the importance of considering EMH in the differential diagnosis of multiple pleural masses.

P2383
Comparative evaluation of alkanine phosphatase (ALP) & adenosine deaminase (ADA) in pleural fluid and serum of patients with pleural effusions Irene Tsilioni, Markos Minas, Vassiliki Tsolaki, Apostolos Triantaras, Christos Daenas, Eirini Geroergiou. Respiratory Medicine Department, University of Thessaly Medical School, Larissa, Greece

Background: High levels of alkaline phosphatase (ALP) and adenosine deaminase (ADA) have been suggested for the discrimination between exudative and transudative pleural effusions (PE).

Objectives: The purpose of this study is to assess the levels of ALP and Adenosine Deaminase (ADA) in the pleural fluid of patients with PE. We also evaluate the usefulness of ALP activity in differentiating transudates from exudates and further in separating tuberculous PE from other causes of exudative effusions (malignant and parapneumonic PE).

Materials and methods: A total of 60 patients, admitted to our hospital, having PE due to various etiologies were included in this study. The patients were divided into four groups according to the final diagnosis: 27 malignant, 19 parapneumonic, 8 tuberculous and 6 transudative PE.

Results: Both mean pleural fluid ALP and ADA values were significantly higher in transudates compared to exudates (61.04±5.86 vs. 32.67±1.42 U/mL; p=0.012 and 39.81±4.83 vs. 8.22±1.45 U/L; p=0.0004 respectively). Parapneumonic and tuberculous pleural fluid ALP and ADA were significantly lower compared to malignant PE respectively. In ROC curve analysis, sensitivity and specificity values were 98.1% and 83.3% respectively for a cut-off value of 9.2 U/L for pleural ADA and 54.7% and 83.3% respectively for a cut-off value of 45 U/mL.

Conclusion: Both ADA and ALP showed the same specificity in distinguishing exudative from transudative PE whereas ADA showed greater sensitivity compared to ALP; although both biomarkers were significantly higher in exudates compared to transudates.

P2384
The impact of malignant pleural effusion – A retrospective review
Richard Budd, Nana Acharya, Muhammad Malik. Respiratory Medicine, Barnsley Hospital NHS Foundation Trust, Barnsley, South Yorkshire, United Kingdom

Barnsley Hospital (BH) serves a population of 220,000 people. The respiratory specialists have noticed a high burden of care associated with the management of pleural disease. An average United Kingdom (UK) district general hospital would expect to diagnose and treat approximately 230 new cases of malignant pleural effusion (MPE) per year [1]. Projected figures suggest an increase of 100,000 cancer diagnoses per year within the UK of which 15% will have an associated MPE [1]. One NHS bed day costs £225 [2] and with this in mind we considered the workload and financial resources required to manage these cases.

Method: We retrospectively analysed data over an 18-month period, searching clinical coding archives using the keyword “pleural effusion”. Cases with a malignancy coded under the heading “primary diagnosis”, “diagnosis 1” or “diagnosis 2” were identified as having a MPE. These cases were reviewed to assess total number of inpatient days, number of patient episodes and length of stay (LOS).

Results: Number of patient episodes for pleural effusion of any cause = 1195 Number of patient episodes for MPE = 226 (including recurrent admissions) Number of MPE secondary to lung cancer = 90 (39.8%) Average LOS for MPE = 7.3 days

Conclusion: The burden of MPE management at BH is significant, considering that in this 18 month period 1650 inpatient days were utilised. By highlighting the financial impact of this data there has been a successful bid by the lead lung cancer specialist for funding of a medical thorascopy service in BH. A recent audit of the medical thorascopy service has confirmed a reduction in LOS and recurrent admissions.

P2840
Desmoplastic small round cell tumour of the pleura. Report of a rare case
Iris Vlachanti1, Evangelia Chomolou1, Margarita Baka2, Helen Kosmidou3,
Mina Gagi1, 2 1 5th Respiratory Medicine Department, 2 Sotira Hospital, Athens, Greece; 3 Oncology Department, “Sotira” Children’s Hospital, Athens, Greece
Background: Desmoplastic small round cell tumour (DSRCT) is a rare, highly aggressive malignancy typically presenting as an abdomen mass. It usually occurs in young population with male predominance.
Aims: To report a rare case of DSRCT arising from the pleura in a 15-year old female.
Methods: We present a clinical case of a young patient who presented with dyspnoea on exertion thoracic back pain and significant weight loss. Physical examination revealed decreased breath sounds of the right hemithorax. A computed tomography scan suggested extended pleural effusion combined with a large pleural mass of the right side extending in the abdomen and paracolic lymphadenopathy. The diagnosis of the mass revealed histological and immunohistochemical characteristics consistent with desmoplastic small round cell tumor. The patient received 7 courses of chemotherapy according to the P6 protocol which involved etoposide, doxorubicin and vincristine for courses 1-3 and 6, ifosfamide and etoposide for courses 4, 5 and 7.
Results: The patient obtained a partial response after completion of chemotherapy and, subsequently, she received local radiotherapy. Eight months after the initial diagnosis the patient remains in a clinically stable condition.
Conclusion: Desmoplastic small round cell tumor is an uncommon aggressive malignancy. It appears to be chemosensitive but response to treatment is only short-lasting. Current literature suggests a multidisciplinary approach including chemotherapy, radiation and surgery. However, prognosis remains poor.

P2841
Miliary mesotheloma: A consequence of trimodality therapy?
Losek Parek, Sophie Larroumagne, Hervé Datau, Philippe Astud. Division of Thoracic Oncology, Pulmonary Diseases, and Interventional Pulmonology, Hôpital Nord – Université de la Méditerranée, Marseille, France
Background: Malignant pleural mesothelioma (MPM) is a rare cancer. Trimodality therapy (TMT) for resectable MPM, combining Cisplatin-based chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant high-dose radiotherapy, is one of the therapeutic strategies with prolonged survival in selective cases. From two recent clinical cases showing dissemination of the disease after multimodal approach, the authors perform a review of the literature trying to find a link between metastatic evolution and aggressive therapeutic strategy.
Case reports: Two patients presenting with chest pain and pleural effusion had MPM considered, after careful preoperative work–up including negative cerebral scans, chest pain at right side of thorax and effort dispnea was hospitalized. A well defined pleural effusion without pleural nodules was observed at chest x-ray. Multiple lymphadenopathies in the mediastinum and a consolidation area of 8 x 10 x 6 cm in size showing air bronchograms in right lung upper and middle lobes medial segment was reported at computed chest tomography.
A mass lesion obliterating the right upper lobe entrance showing sign of spreading to the intermediate bronchus was observed with fiberoptic bronchoscopy.
Classical type of Hodgkin’s Disease was diagnosed by the histopathologic examination of mucosal biopsy specimen confirming a very rarely observed case of primary pulmonary Hodgkin’s disease with endobronchial involvement.

P2844
Experience of an intercostal chest drain training course in the Yorkshire and Humber postgraduate deanery
Georgina Esterbrook1, Tim Sutherland2, Matthew Callister2, James McCreanor1, Joe Hogg1, Peter Smith1, Richard Teoh3, Jack Kastelik 3.
1Respiratory Medicine, Pinderfields General Hospital, Wakefield, West Yorkshire, United Kingdom; 2 Respiratory Medicine, St James’s University Hospital, Leeds, West Yorkshire, United Kingdom; 3Respiratory Medicine, Castle Hill Hospital, Hull, East Yorkshire, United Kingdom
Introduction: A significant number of deaths and cases of serious harm have been reported as a result of the insertion of chest drains. Reasons include poor training and inadequate supervision of trainees. We devised a simulation chest drain insertion course to improve competency and reduce adverse events.
Methods: A half-day course was devised, consisting of a lecture, theory examination, practical simulation session and a competency-based assessment. Emphasis is placed on teaching current guidelines and small group supervised practice on manikins. A certificate of competence is provided for all candidates successfully completing the course. Feedback for each aspect of the course was collected based on a 5 point Likert scale.
Results: Over 18 months, 13 courses took place and 140 feedback forms returned. In over 96% of cases, all aspects were rated as good or very good. The course was praised for the ratio of trainees to candidates, the length of time for practice, the seniority of the trainees and the length of course. A significant number of candidates would recommend the course to a colleague as part of medical training.
Discussion: In our region, this is the first course dedicated to teaching seldinger chest drain insertion. It successfully employs a variety of different educational methods, and provides a ratio of senior trainers to candidates that facilitates learning. In comparison to other practical skills courses, this course dedicates more

P2843
Health care professionals’ knowledges of OSAHS’s diagnosis
PM Prapa1, I. Nikolopoulos1, P. Kyriacou2, Konstantinos Gourgoulianis2.
1Department of Respiratory and Critical Care Medicine, Sotiria Chest Hospital, Athens, Greece; 2Respiratory Medicine Department, University of Thessaly, Medical School, Larissa, Greece
Methods: A questionnaire was designed to explore HPs’ knowledge to identify OSAHS. It was completed by Respiratory Physicians in a Pulmonary Department, by General Practitioners in Primary Care Center and by Primary Care Physicians.
Results: A panel of Respiratory Physicians evaluated the answers.
Results: A total of 138 HPs completed the survey, (53.6% Respiratory Physicians (n=74), 18,8% General Practitioners (n=26), 27,5% Primary Care Physicians (n=38).
The HPs’ education on OSAHS was at University (33,4%), Post graduate (1,4%), Medical literature (66,7%), day-to-day practice (53,6%) and medical residency (40,9%).
The correct answers were for:
– Clinical symptoms: Snoring 78,2%, daytime sleepiness 87%, morning headaches 58% and nocturia 20,3%.
– Complications: hypertension, 73,9%, chronic pulmonary heart disease 43,5% and
– Clinical features: obesity 79,7%, large neck circumference 42%.
Logistic regression analysis revealed that physicians who acquired their knowledge in their day-to-day practice on OSAHS were more likely to answer correct question concerning clinical symptoms (OR=13.12,95%CI: 2.94-58.41, p<0.001) complications (OR=5.73, 95%CI: 2.31-14.23, p<0.001) and clinical features (OR=12.69, 95%CI: 4.87-33.07, p<0.001).
Conclusion: Following this study; education sessions must be introduced in all education level in an attempt to improve the identification of this disorder and to allow the Physicians to take part in the management of OSAHS.

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P2920
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Discussion: In our region, this is the first course dedicated to teaching seldinger chest drain insertion. It successfully employs a variety of different educational methods, and provides a ratio of senior trainers to candidates that facilitates learning. In comparison to other practical skills courses, this course dedicates more
time to individual tuition and practice to thoroughly assess safety and competency. We would recommend that the simulation of trainee chest drain insertion should be available to all trainees in respiratory medicine.

P2845
Clinical impact of a program to educate community pharmacists in providing proper inhalation technique for asthma patients
Masaya Takeamura1, Katsumi Mitsui2, Masako Ido3, Misuzu Koyama4, Masataka Shimotani5, Daiki Inoue5, Kazufumi Takamatu1, Ryo Iotani1, Manabu Ishitoko1, Shinko Suzuki1, Kensaku Aihara1, Hitoshi Kagoi1, Motonari Fukui6, 1Respiratory Disease Center, Tazuke Kofujii Medical Research Institute, Kitano-Hospital, Osaka, Japan; 2Division of Pharmacy, Tazuke Kofujii Medical Research Institute, Kitano-Hospital, Osaka, Japan; 3Division of Pharmacy, Kita-ku Pharmaceutical Association, Osaka, Japan

Background: Currently, more than 10 types of inhaler devices are available in the asthma treatment. The prevalence of these inhalers has resulted in a wide range of choices for clinicians but in confusion for both medical staffs and patients regarding how to use inhaler devices correctly.

Objective: To evaluate the clinical impact of an educational program for community pharmacists to provide repeated instructions of correct and consistent inhalation technique to asthma patients.

Methods: Since 2007, Kitano hospital and Kita-ku Pharmaceutical Association Osaka have provided community-pharmacists with a regular educational program on correct inhaler use once a year. Certified participants have instructed asthma patients to use their inhalers with proper techniques at regular intervals (at least 6 months). We examined the frequency of asthma exacerbations, adherence to inhalation regimen using a 5-point Likert scale questionnaire, and health status assessed by St George’s Respiratory Questionnaire (SGRQ) in asthma patients before starting the program and after four years.

Results: Usable information was obtained from 146 asthma patients at baseline and 143 at 4 years. Compared with baseline values, significant decreases were found in the frequency of asthma exacerbations (1.4±1.6 vs 1.0±1.4 times/year, p=0.042) and emergency room visits (0.5±1.0 vs 0.2±0.5 times/year, p=0.004). Adherence to the inhalation regimen significantly increased (p=0.041), but SGRQ scores unchanged.

Conclusion: A regular program which educates community-pharmacists about how to instruct patients in proper inhaler use may improve asthma control and adherence to patients’ inhalation regimen.

P2846
Quit smoking in pregnancy with asthma
Olga Sukhovskaya, Olga Lavrova, Natalia Kolpinskaya. Research Institute of Pulmonology, Pavlov’s State Medical University, St. Petersburg, Russian Federation

The aim of this study was to identify the factors related to quit smoking during pregnancy in patients with asthma. The sample included 990 pregnant (417 with asthma) in age 18-40 years. They were interviewed about smoking and social status. CO breathing test has been made for cigarette consumption.

Investigation shows that 26.4% pregnancies without asthma were smokers (6.95±0.94 cigarettes per day), 23% pregnant per asthmatic pregnant una were smokers (7.06±1.2 cigarette per day). Before pregnancy women smoked in 57.1% cases without asthma (11.3±1.6 cigarette per day) and in 49.4% with asthma (10.6±1.7 cigarette per day). Education programs for pregnant women with asthma. Health preg-
nants quit smoking in 14.7±1.9 week of pregnancy, patients with asthma – in 8.77±1.2 week. The cessation smoking program included of CO level measuring. The discrepancy of answers and CO levels was in 22% of cases.

The factors, promotional quit smoking during pregnancy were: educational pro-
grams for smokers, non-smoking family (especially husband), high education, support of husband in quit smoking. Unmarried pregnant smokers smoked twice more often than married women. Planned pregnancy contributed to smoking rejection, which was found in the frequency of asthma exacerbations (1.4±1.6 vs 1.0±1.4 times/year, p=0.042) and emergency room visits (0.5±1.0 vs 0.2±0.5 times/year, p=0.004). Adherence to the inhalation regimen significantly increased (p=0.041), but SGRQ scores unchanged.

Conclusion: A regular program which educates community-pharmacists about how to instruct patients in proper inhaler use may improve asthma control and adherence to patients’ inhalation regimen.

P2847
Competency assessment of foundation year 1 doctors in the prescription and use of oxygen
David Tarpey, Diana Lees, Ana De Ramon. Respiratory Medicine, Warrington General Hospital, Warrington, Cheshire, United Kingdom

Introduction: Oxygen is a commonly used drug in hospital medicine, with at least 25% of ward based patients receiving it at any one time. The UK National Patient Safety Agency (NPSA) report on oxygen therapy in hospitals (2009) detailed over 200 incidents due to inappropriate oxygen prescription, with a subsequent mandate that all oxygen should be prescribed as per national guidelines.

Aim: To assess competency levels in Foundation year 1 (F1) doctors in oxygen prescription in our hospital trust.

Method: A questionnaire was completed at the beginning of the F1 year, to assess understanding of oxygen prescription. This was repeated 6 months later following teaching sessions and clinical experience.

Results: 22/50 (73% of F1 doctors) took the survey with a mean score of 58% (range 40-80%). 18 (60% of the original cohort) took the test six months later with a significantly decreased mean score of 47% (range 50-80%) p=0.04. Improvement was seen in the use of emergency oxygen in patients with normal saturations (45% vs 78%), on oxygen prescription (63% vs 100%) and in the correct procedure for stopping oxygen (45% vs 55%). Persistent knowledge gaps were seen with target saturations (72% to 70%) and increasing flow rates to match patient needs (32% vs 22%).

Conclusions: Results demonstrate a lack of knowledge of national guidance amongst junior doctors. Improvement was demonstrated following teaching sessions and clinical experience. Future teaching sessions should focus on areas where improvement was not seen to increase adherence to guidelines and improve patient care.

P2848
Does a training programme in chest drain insertion improve patient safety?
Theodora Vatopoulou1, Chirag Dave2, Amanda James2, Dwight McLeod3
1Respiratory Department, Sandwell Hospital, Birmingham, United Kingdom; 2Respiratory Department, Heartlands Hospital, Birmingham, United Kingdom

Introduction: Following the National Patient Safety Agency alert for intercostal chest drain (ICD) insertion, our respiratory department introduced a training programme for all registrars (SpRs) & junior doctors. Emphasis was placed on completing a proforma at the time of insertion & notifying our team, so that subsequent close monitor of the ICD management occurred.

Methods: A retrospective study of 52 consecutive ICD insertions notified at Sandwell Hospital over a year (Jan09-Jan10, males 80%, median age 67 years) was conducted. Indications for drainage, technique, documentation & complications were audited. The results were compared with a previous departmental 6 month audit.

Results: Medical SpRs inserted 12 (23.07%), respiratory SpRs & senior house officers (SHOs) 24 (46.15%), other SHOs 3 (5.7%), consultants 6 (11.5%), house officers 1 (1.9%) & in 6 (11.5%) the grade was unknown. 21 (40%) were inserted out of hours, 22 (42%) on the respiratory ward. Type of drain: 49 Seldinger (94.2%), 2 blunt dissections (3.8%), 1 pigtail (1.9%). All indications were according to the British Thoracic Society guidelines, 21 pneumothoraces (40%), 29 pleural effusions (55%) & replacing 2 blocked ICDs (5%). The average length of ICD in situ 3.4 days compared to 5.2 previously. Complications included 1 empyema & 3 drains fell out. In the earlier audit, complications included ICD insertion into a bulla, 1 insertion into the liver, 2 severe site infections & 2 re-admissions for empyema.

Conclusions: ICD training programmes improve patient safety. As over half of ICDs are placed by non-respiratory junior staff, there is a continual need for training. However, this is not just about ICD insertion, post insertion care, prompted by the proforma reduces complications & length of ICD stay.

P2849
Effect of training in educational programs at the level of control and quality of life of patients with bronchial asthma
Olena Semenyayeva1, Nadiya Monogorova1, Denys Stupchenko2, Alexandr Le3
1Internal Medicine named after A.Y.Gubergerits, Donetsk National Medical University; 2Department of Thoracic Surgery, Donetsk Regional Clinical Territorial Medical Union; Donetsk Ukraine; 3Department of Pulmonology, Donetsk Regional Clinical Territorial Medical Union, Donetsk, Ukraine

Objective: To study the effect of educational programs, training in asthma-school
P2850
The use of lambs chests in chest drain insertion simulation
Alasadair Nazeralli-Maitland1, Mitchell Goldenberg2, Nadim Iwaw2, 1Department of Internal Medicine, Queen’s University, Kingston, ON, Canada; 2Undergraduate Medicine, St. George’s University of London, London, United Kingdom

In an attempt to familiarize medical trainees with chest drain insertion, we sought to find a successful way of instructing students with its insertion technique. Students were given a thirty-minute lecture on chest anatomy, indications for insertion and then the insertion was demonstrated. Students were then taught the Seldinger (tube over guide-wire) technique and also the surgical drain (directly-visualized) insertion technique in a one-hour lab session. No direct comparison was made between other popular simulation mediums (such as plastic models or pork back ribs) nor were students subsequently directly observed inserting tubes on actual patients. The students were instructed then monitored and scored on successful insertion in the pleural space by an examiner informally. In discussion it was felt that the tactile feedback from the lamb’s carcasses demonstrated outstanding anatomical correlation and also demonstrated similar difficulties to human chest drain insertion. Both the anterior & mid-axillary lines were clearly visualized as well as the costal margins. There was also the opportunity to demonstrate administration of local anesthetic agents as well as one of the most common pitfalls of chest tube insertion: hitting the bone. The session was received very well with feedback revealing an appropriate amount of time spent on both instruction and demonstration. Lamb’s thoraces are a superb medium for simulation-based instruction of chest tube insertion. The use of an animal model has its benefits with respect to anatomical realism and the tactile realism of feeling actual muscle and bone. It likely provided a good stepping-stone between abstract classroom instruction and hospital patient insertion.

P2851
An assessment of physicians knowledge of the GINA guidelines
Victor Umoh1, Effiong Akpan2, Anthony Akula2, Danlaye Alasa2, John Ekoet1, 1Department of Internal Medicine, University of Uyo, Uyo, Akwa-Ibom State, Nigeria; 2Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria

Introduction: The Global Strategy for Asthma Management and Prevention (GINA) is useful in the management of asthma patients. Aims:
To compare the knowledge about IT in patients (Pts) with asthma or COPD, who were treated before and one year after the education was given.
Methods: We hypothesized that many physicians who attend to asthma patients are not familiar with the components of the GINA guidelines.
Methods: Based on the GINA guidelines, a multiple choice questionnaire which addressed various components of the guidelines was distributed to physicians who attend to asthma patients.
Results: 54 Physicians were randomly selected from among 118 physicians from 2 Teaching Hospitals in Nigeria: 51 from Internal medicine, 20 from Family Medicine and 3 from Respiratory unit. There were 10 general internists, 2 medical officers, 28 junior residents, 11 senior residents and 3 consultants. 72.2% of the respondents did not attend any Continued Medical Education (CME) in asthma after graduation. Those of them who attended a CME post graduation scored higher than those who had not attended but this was not significant (39.7% Vs 31.2%). There was also an improvement in total performance with hierarchy but this was not statistically significant. Respiratory physicians scored significantly higher than the Internal medicine and the Family physicians (70.96% Vs 34.13% Vs 37.09%). The knowledge of pathological basis of asthma had the highest sub-score (50%) followed by diagnosis (48.7%) with asthma education having the least score (16.6%). Overall the average total score was poor (37.2%).
Conclusion: By identifying the areas of deficiency in each group of Doctors we can design education intervention programmes to improve the understanding of the GINA guidelines among physicians and ultimately the quality of care.

P2852
Patients’ knowledge about inhalation therapy in pulmonology – One year after intervention
Ljudmila Nagorni-Obradovic, Dragica Posut, Dejana Vukovic, Jovana Maskovic. Internal Medicine, School of Medicine University of Belgrade, Belgrade, Serbia Social Medicine, School of Medicine University of Belgrade, Belgrade, Serbia Intensive Care Unit, Teaching Hospital of Lung Diseases, Belgrade, Serbia

Background: Inhalation therapy (IT) is important in successful treatment in pulmonology.
Aim: To compare the knowledge about IT in patients (Pts) with asthma or COPD, before and one year after the education was given.
Method: In January 2010 and January 2011, we used anonymous self created six-questions questionnaire to interview the same group of 56 Pts who were treated with IT at University hospital (average age 56±12 years). We used McNemar test for statistical analysis.
Results: The number and proportion of Pts with correct technique or positive answers is shown in Table where p<0.01 = significant difference; NS = not significant.

Table 1 - Results

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<td>1. Showed correct technique of using IT</td>
<td>20 (35.5)</td>
<td>30 (50)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2. IT is only for severe degree of disease</td>
<td>18 (32.1)</td>
<td>10 (17.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3. IT consists of various types of drugs</td>
<td>16 (28.6)</td>
<td>19 (33.9)</td>
<td>NS</td>
</tr>
<tr>
<td>4. It is possible to add it to IT</td>
<td>17 (30.4)</td>
<td>12 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>5. Treatment interruption by Pts's decision</td>
<td>24 (42.8)</td>
<td>22 (39.2)</td>
<td>NS</td>
</tr>
<tr>
<td>6. Do not make difference between use of short and long acting β2 agonists</td>
<td>40 (71.4)</td>
<td>38 (67.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions: One year after education, the Pts significantly corrected their technique of using IT and their misconception about using IT only in severe degree of disease is decreased. Although improved, the knowledge related to the other items requires further patients’ education.

P2853
Audit of intervention to improve educational experience in a respiratory medicine department
Zoe Pond. Department of Respiratory Medicine, Queen Alexandra Hospital, Portsmouth, United Kingdom

Introduction: A continuing rise in service pressures and reduced working hours creates an ever increasing challenge in the provision of a good quality training experience for junior doctors. Objectives: The aims were to determine trainees’ perception of the education in their current post, provide opportunity for suggestions for improvement, make changes and then assess the effectiveness of changes made. Methods: All juniors within the department were asked to complete an anonymous questionnaire, covering educational aspects of their post, within the last few weeks of July 2010. This was repeated in November to assess the impact of changes made.
Results: Response rates of 87.5% (14/16) and 85% (17/20) were obtained with all grades represented. Training was rated fair to excellent. The most useful educational experience for the more junior doctors, in both audits, were on call duties where they were managing conditions they had not previously encountered. The more senior trainees found ward rounds most helpful. Areas for improvement identified in the first audit included enabling juniors to attend grade-specific teaching, increasing ward round teaching, and increasing opportunities for workplace based assessments. Following implementation of changes, 62.5% reported workplace based assessments gave useful feedback compared to 36% previously. Attendance at grade-specific teaching increased from 57% to 89% in more junior trainees. All grades commented on the usefulness of this teaching as it was targeted at their level. Conclusions: Surveying trainees regarding their educational experience is useful and can allow focussed intervention to improve areas of respiratory education.

P2854
Audit on pleural procedure in UK district general hospital
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Introduction: Intercostal Chest Drain (ICD) insertion is an invasive procedure indicated in certain emergency and elective scenarios. The practice is changing with more importance given to training, safety and use of ultrasound imaging guidance. Aims: The aim of this audit was to access current awareness & training level of junior doctors and level of practice. Methods and results: First part of audit includes questionnaire survey on awareness and competency of the 26 respondent, 61% were independently competent at ICD insertion, but only 9% of them performed more than 10 procedures in last one year. Only 23% of doctors had thoracic ultrasound training. In the second part, 38 consecutive cases were audited retrospectively (male = 76%, female = 24%) Pleural effusion (59%) and pneumothorax (31%) accounted for most of the indications. 38% of the procedures performed out of hours and all of them were justified. Only 68% had any form of consent documented. Majority (85%) were inserted by senior doctors (ST3+) level. Bedside Ultrasound was used in 80% of pleural effusion cases. The nursin drainage observation chart was maintained in 88% cases. 8% minor immediate complication reported, no death or organ damage directly related to the procedure. Discussion: This audit has demonstrated improving safety awareness that includes, most of procedure performed by trained doctors and use of bedside ultrasound. But it has highlighted lack of training at junior doctors level, including thoracic ultrasound. Following this audit we have introduced the safety check list and training programme for junior doctors including thoracic ultrasound technique.

References:
P2855
High-fidelity in-situ simulation – A novel training modality for non-invasive ventilation

Introduction: Non-invasive ventilation (NIV) is an expanding treatment modality requiring staff experience and training to ensure clinical effectiveness. Non-specialist junior doctors and nurses often have infrequent exposure to NIV thereby limiting confidence. Patients requiring NIV are often critically unwell and effective crisis resource management (CRM) skills (e.g. communication, leadership, task delegation) are often critical in achieving patient compliance and formulating clear treatment plans. For these reasons, high-fidelity simulation provides an opportune training modality where trainees can practice in a safe “real” setting to increase self-confidence and develop key CRM skills.

Method: We designed an “in-situ” high-fidelity simulation-training module where trainees partake in pre-designed undisclosed scenarios leading a multidisciplinary team involving a nurse blind to the scenario and faculty “plants”. Scenarios are constructed to provide challenging clinical and ethical situations pushing trainees abilities to promote key skills at a registrar level. Candidates used a 6-point Likert Scale questionnaire to self-analyse their performance and learning post-simulation.

Results: Pilot results show trainees have found the module improves confidence in managing respiratory failure requiring NIV when added to a standard training programme. The module additionally develops trainee insight into their situational awareness as well as key communication, clinical decision-making, leadership and team-working skills enabling a structure for future focused improvement.

Conclusions: High-fidelity simulation can be used as an effective training tool as part of a comprehensive NIV training programme.

P2856
Continuing medical education: A contribution of the pneumologists in the pre-hospital medicine
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Until now in Tuscany, the doctors of the Ambulance Service 118 originate from general practitioners after specific qualifying courses, usually directed by resuscitators. In 1999, in Italy, was activated the Continuing Medical Education (CME) and in 2002 the Tuscan Region acknowledged the provisions in the matter. As our ambulance patients present a considerable number of low oxyhemoglobin saturations (Olti et al., ERI 2003: 44, 381), formative events in respiratory diseases were carried out, involving specialists in respiratory medicine as teachers. The training is composed of a series of seminars, including the use of mechanical ventilators during ambulance transfers, alternative devices to intubation, CPAP and non invasive ventilation, oxygen therapy. Formative events were enrolled in 4 hours meetings. At the end of meetings, learning and approval tests were carried out, for acquire the CME credits. Participants had to replay correctly at least the 80% of the questions and to attend the lesson’s time. Moreover 2 short meetings of 2 hours each, were carried out and related to some aspects of respiratory fatigue and spontaneous pneumothorax. 382 hours of specialized formation, the 9% of all the formative hours dispensed from 2003 to 2010 by our Service, were delivered. 100% of the participants found interesting the treated topics; 98.9±1.9% found them useful in theory and the 98.3±6.9% in practice.

Besides the good results in CME credits, 1 point each hour, important concepts and techniques, from the point of view of the pneumologists were explained, showing a further vision of the respiratory emergencies and their management in the pre-hospital medicine.

320. COPD: mechanisms and biomarker

2931
Association of testosterone level with phenotypic characteristics and long-term outcomes of men with COPD in the ECLIPSE cohort

Introduction: The contribution of anti-elastin immunity in COPD is subject of intense debate. Conflicting data are reported on the presence of serum auto-antibodies against elastin fragments correlating with COPD severity. As auto-immunity is driven by antigen-specific T cells, we investigated the presence of B cell and T cell responses against elastin fragments in a large sample of COPD patients and controls.

Material and methods: Anti-elastin antibodies were analyzed using indirect ELISA on plasma samples of 352 COPD patients (GOLD I-4) and 168 age-matched smoking controls. In a random subset of 25 patients, T-cell responses against elastin fragments were further determined with ELISPOT (IFN-γ and IL-2) on peripheral blood mononuclear cells (PBMC) and compared with responses of 5 non-smoking age-matched controls.

Results: Increased titers of anti-elastin antibodies were found in 14.2% (24/168) of smoking controls compared to 12.5% (44/352) of the COPD population (p=0.07).

3923
Relation of health-related quality of life, frequent exacerbation phenotype and circulating systemic biomarkers in stable COPD
Daiana Stolz1,2, Francesco Blass1, Renaud Louis1,5, Wim Janssens3,4.

Introduction: Non-invasive ventilation (NIV) is an expanding treatment modality in managing respiratory failure requiring NIV when added to a standard training program. In an univariate analysis, age, sex, smoking status, chronic obstructive pulmonary disease severity, number of exacerbations, number of hospitalizations, and body mass index (BMI) were positively correlated with the proportion of time spent in NIV. In a multivariate model, the percentage of time spent in NIV was significantly associated with BMI and number of exacerbations. However, the percentage of time spent in NIV was not significantly associated with the proportion of time spent in the upper lobes or the lower lobes. This finding suggests that the distribution of NIV is more frequent among patients with higher BMI and lower BMI, respectively. Therefore, a randomized controlled trial (RCT) comparing the effects of NIV and conventional treatment in patients with COPD is warranted to further investigate these findings. In conclusion, NIV is a valuable treatment option for patients with COPD who experience respiratory failure, and the benefits of NIV can be optimized by selecting patients with higher BMI and lower BMI.
No significant correlation was found between anti-elastin antibodies and FEV1% predicted (p=0.699), nor with the presence of emphysema on CT scan (p=0.150). Despite significant responses to control antigen, ELISPOT analysis could not detect increased T cell responses against elastin in any of the individuals.

**Conclusion:** Anti-elastin antibodies are not specific for COPD patients and do not correlate with disease severity. The absence of elastin-specific T cell responses further weakens the role of anti-elastin auto-immunity in the pathogenesis of COPD.

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2936

**Can brain MRI explain cognitive decline in COPD? A pilot study**

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**Background:** Cognitive deficits have been described in patients with COPD. We used MRI to investigate brain structure in COPD patients with and without evidence of cognitive decline and in healthy control subjects.

**Methods:** Participants (n=27) completed a full cognitive assessment and MRI scan. Two groups of COPD patients were selected; those who demonstrated evidence of cognitive decline (COPD-D; n=9) or who did not (COPD-N; n=9). Age-matched healthy controls (HC; n=9) were studied. Volumes of grey matter (GMV), white matter (WMV), and white matter lesions were calculated. The presence of lesions in the brain stem (BSL) and external capsule (ECL) was noted.

**Results:** Groups did not differ on measures of GMV or WMV. LV was significantly greater in patients versus controls (t=3.47; p=0.002); there was no difference between LV in COPD-N and COPD-D (t=3.42; p=0.737). No significant group difference in the presence of BSL was observed (X2(df=3)=0.0; p=0.223), but ECL was numerically more frequent in the COPD-D group (X2(df=4)=5.64; p=0.060).

See Table 1.

<table>
<thead>
<tr>
<th>Age, years: Mean (SD) Range</th>
<th>Controls (n=9)</th>
<th>COPD-N (n=9)</th>
<th>COPD-D (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70 (10) 57–88</td>
<td>70 (7) 60–82</td>
<td>70 (8) 60–81</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>6 / 3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>GMV, mm3</td>
<td>736,164 (39,035)</td>
<td>741,856 (49,877)</td>
<td>729,649 (47,252)</td>
</tr>
<tr>
<td>WMV, mm3</td>
<td>683,854 (60,910)</td>
<td>668,437 (29,210)</td>
<td>686,654 (47,078)</td>
</tr>
<tr>
<td>LV, mm3</td>
<td>4,891 (356)</td>
<td>18,220 (14,979)</td>
<td>15,901 (13,734)</td>
</tr>
<tr>
<td>% BSL</td>
<td>11%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>% ECL</td>
<td>22%</td>
<td>44%</td>
<td>77%</td>
</tr>
</tbody>
</table>

**Conclusion:** COPD-D and COPD-N patients both have more white matter lesions than HC, possibly due to increased vascular risk. The significance of BSL and ECL requires further exploration. Future analysis will use methods that detect change in tissue microstructure, and associations between brain damage and cognition.

2937

**Iron deficiency in non-anemic patients with chronic obstructive pulmonary disease**

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**Background:** Iron deficiency contributes to reduced exercise capacity in patients with heart failure. The repletion of iron improves cognitive, symptomatic, and exercise performance in these patients independent of hemoglobin. COPD shares many functional features of heart failure. Thus iron deficiency could be a potential therapeutic target in COPD.

**Aims and objectives:** The aim of this study was to determine the prevalence of iron deficiency in non-anemic patients with COPD.

**Methods:** Serum markers of iron status were measured in 53 stable non-anemic (hemoglobin>12 g/L) COPD patients (53% males; mean age 64±8 years, mean FEV1 predicted 41±18%; GOLD stage II, III, and IV was 34%, 32%, and 34%, respectively). Iron deficiency was diagnosed when the serum ferritin level was either <100 μg/l or was between 100 and 299 μg/l with the transferrin saturation <20%. Results: The serum ferritin level was <100 μg/l in 20 patients. The serum ferritin level was between 100 and 299 μg/l and transferrin saturation was <20% in 6 patients. Thus iron deficiency was present in 49% of the patients. The median soluble transferrin receptor to log_ferritin ratio was higher in patients with iron deficiency (1.7, 1.0 to 1.4) compared to patients without (1.7, 1.4 to 2.0), p=0.001.

**Conclusions:** Iron deficiency is present in half of the patients with stable COPD. A randomized, placebo-controlled trial should clarify whether repletion of iron stores improves functional performance in COPD patients with iron deficiency.
321. Barrier functions in sepsis and acute lung injury

2938 TNF-α-induced septic shock is attenuated in acid sphingomyelinase-deficient mice
Lucy Kathleen Reiss¹, Yang Yang¹, Dieter Adam², Stefan Uhlig¹. ¹Institute of Pharmacology and Toxicology, Medical Faculty of RWTH Aachen University, Aachen, Germany; ²Institute of Immunology, Christian-Albrechts University, Kiel, Germany

TNF-α plays a major role as mediator of acute inflammation and apoptosis. Surprisingly, little is known about the effects of high plasma levels of TNF-α on the lung. Previous studies revealed that TNF-α causes lethal depression of systemic circulation including hypotension. The aim of this study was to investigate the pulmonary effects of TNF-α in mechanically ventilated mice. Further, the role of caspases and acid sphingomyelinase (ASMase) was examined.

C57BL/6 wild type and ASMase-/- mice received TNF-α intravenously; in addition, half of the animals were treated with the caspase inhibitor zVAD-fmk. All mice were ventilated for 6h at V1=8mL/kg and f=180/min⁻¹ with FiO2=0.3 and PEEP=2cmH2O while lung functions were followed by the forced oscillation technique. In order to reduce mortality due to septic shock, saline was given via an arterial catheter and body temperature was stabilized at 37°C. Blood gases, lung histology, pro-inflammatory mediators and microvascular permeability were examined. Fluid support and stabilization of body temperature were sufficient to avoid lethal septic shock. Sepsis was indicated by high serum levels of pro-inflammatory mediators and metabolic acidosis. TNF-α decreased blood pressure and increased heart rate in wild type mice. ASMase-/- mice were protected from the cardiovascular effects, but caspase inhibition had no influence. Although high levels of TNF-α were detected in the lung, no severe pulmonary inflammation or alteration of lung functions was found. We conclude that septic shock caused by high circulating levels of TNF-α is partly mediated by ASMase. However, TNF-α alone is not sufficient to cause acute lung injury in ventilated mice.

2939 Pulmonary epithelial CCR3 promotes LPS-induced lung inflammation by mediating release of IL-8
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Objectives: Interleukin (IL)-8 from pulmonary epithelial cells has been suggested to play an important role in the airway inflammation, although the mechanism remains unclear. We envisioned a possibility that pulmonary epithelial CCR3 could be involved in secretion and regulation of IL-8 and promote Lipopolysaccharide (LPS)-induced lung inflammation.

Methods: Human bronchial epithelial cell line NCI-H292 and alveolar type II epithelial cell line A549 were used to test role of CCR3 in production of IL-8 at cellular level. In vivo studies were performed on C57BL/6 mice instilled intratracheally with LPS in a model of acute lung injury (ALI). The activity of a CCR3-specific inhibitor (SB-328437) was measured in both in vitro and in vivo systems.

Results: We found that expressions of CCR3 on NCI-H292 and A549 cells were increased by 23% and 16%, respectively, 24 h after the challenge with LPS. LPS increased IL-8 productions in NCI-H292 and A549 cells, which were inhibited significantly by SB-328437. SB-328437 also diminished neutrophil recruitment in alveolar airspaces and improved LPS-induced ALI accompanied with reduction of IL-8 secretion in bronchoalveolar lavage fluid.

Conclusions: These results suggest that pulmonary epithelial CCR3 be involved in progression of LPS-induced lung inflammation by mediating release of IL-8. CCR3 in pulmonary epithelia may be an attractive target for development of therapies for ALI.

2940 Lipopolysaccharide attenuates endothelial barrier function through a pp60src mediated inhibition of dimethylaminohydrolase (DDAH)
Saurabh Aggarwal, Shrutti Sharma, Sanjiv Kumar, Stephen Black, Yali Hou.
Vascular Biology Center, George Health Sciences University, Augusta, GA, United States

Acute lung injury is a severe hypoxemic respiratory insufficiency associated with alterations in lung structure and function. Previously, we found that LPS increases the activity of the DDAH in the lung endothelium and that LPS attenuates the DDAH activity. We examined the pp60src mediated inhibition of DDAH activity in human lung microvascular endothelial cells (HLMVEC). In this study, we elucidated the mechanisms involved in the attenuation and prevention of DDAH2 by LPS. Utilizing an electric cell impedance sensing apparatus, we found that the overexpression of DDAH2 in human lung microvascular endothelial cells (HLMVEC) prevents the LPS (1 endotoxin unit/ml) induced decrease in transendothelial resistance. Further, we found that the overexpression of a dominant negative mutant of pp60src attenuated the LPS mediated decrease in DDAH activity and increased ADMA levels without altering expression of DDAH2 protein levels. Further, LPS increased the interaction between DDAH2 and pp60src and also increased its tyrosine phosphorylation. In the LPS treated mouse lung, we found that the decrease in DDAH activity correlated with an increase in LPS mediated interaction of DDAH2 and tyrosine phosphorylation of DDAH2. Finally, the overexpression of DDAH2 in mouse lung endothelial cells, using a polyethyleneimine (PEI) based transfection reagent, led to an increase in DDAH activity, a decrease in ADMA levels, and the attenuation of the LPS mediated increase in the lung leak as measured by extravasation of Evans blue dye. The prevention of DDAH activity in the lung endothelium may provide new insights for the prevention of LPS induced ALI.

2941 Role of ADAM17 in endotoxin-induced pulmonary inflammation
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Acute lung injury is associated with enhanced vascular permeability and leukocyte recruitment. Several proinflammatory, soluble and surface-expressed mediators, including TNFα, TNFR1/2, amphiregulin, IL-6R, IL-1R, L-selectin, CXCL11, and JAMs may become released by the activity of the metalloproteinases ADAM10 and ADAM17. We examined the role of these proteases in vascular permeability and leukocyte transmigration in vitro by pharmacological inhibition and lentiviral-mediated siRNA knockdown of ADAM10 and ADAM17. In vivo role of these proteases was studied in a murine model of LPS-induced lung injury by pharmacological inhibition. The relevance of ADAM17 was further analyzed by knockdown of ADAM17 in endothelial or smooth muscle cells. The BAL protein levels and the wet/dry-ratio served as markers of vascular permeability and edema formation. Cell recruitment to the alveolar space and lung tissue was analyzed by flow cytometry; cytokines were determined by ELISA. In vitro, transmigration of neutrophils to IL-8 through pulmonary endothelial cells was reduced by pharmacological inhibition as well as knockdown of ADAM10 or ADAM17. LPS-mediated inhibition of permeability was reduced by pharmacological inhibition, but not by ADAM10 knockdown, indicating a predominant role of ADAM17 in the regulation of endothelial permeability. In vivo, LPS challenge increased the wet/dry-ratio as well as the BAL levels of protein, TNFA, IL-6 and leukocytes. All these effects were largely prevented by inhibitor application or by knockdown of ADAM17 in smooth muscle or endothelial cells. These results indicate that local ADAM17 is involved in the onset of inflammation and tissue injury during endotoxin-induced lung inflammation.
We have previously reported that NADPH oxidase 1 (NOX1) deficiency prevented hyperoxia-induced acute lung injury in mice and played an essential role in cell death of mouse alveolar epithelial cells (Carnesecchi, S. et al., AJCCM, 2009; 180: 972-981). In order to determine the mechanisms by which NOX1 induces epithelial cell death during hyperoxia, we specifically knocked-down NOX1 in a pulmonary epithelial cell line (MLE-12) using a lentiviral vector strategy. Our results show that NOX1 mRNA was reduced by 35% after hyperoxia compared to scramble sRNA (control cells). Hyperoxia-induced ROS production was inhibited by 36% in transfected MLE-12 compared to control cells. In addition, we demonstrated that NOX1 deletion leads to less hyperoxia-induced cell death and lyzed by lactate dehydrogenase release, TUNEL staining and decreased cleaved caspase 3. Hyperoxia-induced ERK phosphorylation, a MAPK involved in cell death signaling was inhibited in NOX1-transfected cells. These data show that NOX1 inhibition decreases hyperoxia-induced ROS production and cell death in an epithelial cell line through ERK signaling pathways. Furthermore, to determine whether NOX1 is also involved in human, we studied NOX1 expression in lungs of ARDS patients by using immunostaining. We found that NOX1 was highly expressed in alveolar type II cells of patients suffering from ARDS in particularly in the exudative and organizing stages of the disease. This study is the first direct demonstration that NOX1 is of crucial importance in ARDS and might be responsible for the damage occurring in epithelial type II cells.

2943
Conditioned medium from human mesenchymal stem cells restores both amiloride-sensitive sodium transport and epithelial permeability to protein across alveolar epithelial cell monolayers in an in vitro model of alveolar injury

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Patients with acute lung injury (ALI) have a decreased capacity to reabsorb alveolar edema. Alveolar fluid clearance results from the electro-osmotic gradient created by active sodium (Na+) transport across alveolar epithelium. In various models of ALI MSCs reduce pulmonary edema and increase survival in mice, but in some studies, MSC conditioned medium (MSC-CM) was as effective as MSCs themselves. However, the mechanisms of MSC-CM beneficial effects remain unclear. Thus, in this study our objective was to test the effects of the human MSC-CM on ventialtional transport and epithelial permeability in injured alveolar epithelial cells (AEC). After 18 h of exposure to both hypoxia (3% O2) and 25 mg/ml corin (IL-1β), TNFα and INFγ (CYTHX4), there was an increase in epithelial permeability measured by radio-labeled albumin over 12 h (1.61±0.40 vs 4.7±2.3, p<0.05) and a marked decrease in transepithelial Na transport (4.2±0.3 vs 1.7±0.4 µA/cm², p<0.05). After permeabilization of the basolateral or apical membrane, we showed no change in Na-K-ATPase activity. We then tested the effect of MSC-CM and found that AEC that were exposed to CYT-HX in the presence of MSC-CM (i) completely prevented CYT-HX-induced increase in protein permeability; (ii) restored the amiloride-sensitive ISc, and (iii) increased Na,K-ATPase activity.

2944
Epigenetic regulation of alveolar ion transport

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The Na-K-ATPase regulates alveolar ion transport and fluid balance in the lung, generating the driving force for alveolar fluid clearance (AFC). Transforming growth factor (TGF-β) is a mediator of acute lung injury (ALI), and impacts AFC. It was hypothesised that TGF-β influences Na-K-ATPase function by controlling subunit expression and stoichiometry. The ATP1B1 subunit of the Na-K-ATPase regulates cell-surface stability of the heteromeric Na,K-ATPase complex. Quantitative RT-PCR analysis revealed downregulation of the ATP1B1 gene both in the lungs from ALI patients (4-fold; p<0.05) and lungs from bleomycin-treated mice which developed ALI (2.1-fold; p<0.002). We tested the effect of MSC-CM and found that AEC that were exposed to CYT-HX in the presence of MSC-CM (i) completely prevented CYT-HX-induced increase in protein permeability; (ii) restored the amiloride-sensitive ISc, and (iii) increased Na,K-ATPase activity.

2945
Antitumor activity of MEK and PI3K inhibitors in malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy, and there is no accepted standard therapy for this disease. Objective: We investigated the role of mitogen-activated protein kinase kinase (MEK) inhibitor and phosphatidylinositol 3-kinase (PI3K) inhibitor as targeted therapies for MPM. Method: We examined the therapeutic efficacy of the MEK or PI3K inhibitor against human MPM cell line EHMES-10 both in vitro and orthotopically inoculated into severe combined immunodeficient (SCID) mice. In addition, the molecular mechanisms of these agents were confirmed in vitro and in vivo experiments. Results: MEK or PI3K inhibitor suppressed the growth of MPM model in dose dependent manner both in vitro and in vivo studies. In addition, combining MEK inhibitor with PI3K inhibitor resulted in an additive growth inhibitory effect. EHMES-10 cells showed increasing the G1 cell cycle arrest and apoptosis by treatment of MEK or PI3K inhibitor in vitro. Western blot analysis in vitro and in vivo study showed increasing the p29βH1 and cleaved PARP expression and decreasing the Cyclin E, CyclinD1 and procaspase 3 expressions. In addition, these agents decreased the expression of hypoxia-inducible factor 1α and vascular endothelial growth factor, which play an essential role in tumor angiogenesis and progression. Conclusion: Our results suggest that MEK or PI3K inhibitor is a promising therapeutic strategy, and also provide a basis for useful combination of MEK and PI3K inhibitors in patients with MPM.

2947
mTOR inhibition blocks tumor growth and pleural fluid accumulation in experimental murine mesothelioma

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mTOR is up-regulated in malignant mesothelioma. We aimed to evaluate the effect of Temsirolimus, an mTOR inhibitor, in vivo models of the disease. AE17 and AB1 murine mesothelioma cells were injected into the right flank of syngeneic mice (C57BL6 and BALB-c, respectively) to create subtractaneous tumors. C57BL/6 mice were injected intraperitoneally with AE17 cells to create pleural tumors and effusions. Animals were treated with Temsirolimus (20mg/kg) or vehicle, 5 days/week starting when tumors become palpable (flank model) or on days 8-12 of pleural tumors and effusions. Animals were treated with Temsirolimus (20mg/kg) or vehicle, 5 days/week starting when tumors become palpable (flank model) or on days 8-12 of pleural tumors and effusions. Among mice with AE17 flank tumors, the mean ±SEM tumor volume at day 26 was 1261±383mm³ in control and 383±86mm³ in treated animals (p<0.001). Among mice with AE17 flank tumors, the mean ±SEM tumor volume at day 26 was 1261±383mm³ in control and 383±86mm³ in treated animals (p<0.001). In the AB1 flank model, tumor volume was 1197±253mm³ in control and 174±76mm³ in treated animals (p=0.026). Among mice with pleural AE17 tumors, the mean ±SEM pleural fluid volume at day 15 was 532±19mmicroL, in control and 240±43microL, in treated animals (p=0.018). The mean ±SEM pleural tumor weight was 739±72mg in control
2948 Epigenetic deregulated translation control of C/EBP-alpha leads to increased mesothelioma cell proliferation
Jun Zhong1, Nicola Miglino1, Michael Tammi1, Didier Lardinois2, Lukas Bubenrost1, John Szilard1, Michael Roth1, 1Pulmonary Cell Research & Pneumology, Dept Research and Internal Medicine, University Hospital Basel, Basel, Switzerland; 2Thoracic Surgery, University Hospital Basel, Basel, Switzerland; 3Dept. Pathology, University Hospital Basel, Basel, Switzerland; 4The Woolcock Institute of Medical Research, University of Sydney, Sydney, NSW, Australia

Malignant pleural mesothelioma (MM) resists all available anticancer therapies. A major pathology of MM is the uncontrolled cell proliferation and the fast local spreading with rare metastasis. Therefore the inhibition of proliferation is a major therapeutic target. Proliferation of MM cells was linked to mitogen activated protein kinase (MAPK) activity. In this study we characterised the regulation of MAPK regulated CAA/ET/ENHancer binding proteins (C/EBP) and their role in MM cell proliferation. In five human MM cell lines, cytotoxic and nuclear protein expression was determined by immuno-blotting and immuno-chemistry in tissue sections. Transcription of C/EBPβ was downregulated by real time PCR and translation by a translation reporter assay. We observed a cell compartment specific expression pattern of p38-α, -β and -γ and MAPK in MM cells. Erk1/2 and p38 MAPK together up-regulated the expression of C/EBP-β and -γ, while C/EBP-α was not expressed. Compared to mesothelial cells C/EBP-α translation was reduced in MM, while the mRNA was constitutively expressed. MM cells expressed a relative high level of the C/EBP-α translation suppressor calreticulin, while eIF4E was not significantly modified. Cell proliferation was inhibited by either the blockade of Erk/2, or p38-γ and -α MAPK, or C/EBP-β. Transfection with a C/EBP-α vector reduced proliferation and increased the MM cell’s sensitivity to steroids. Our data implies that in human MM cells an epigenetic mechanism deregulates the translation control of the cell differentiation factor C/EBP-α which leads to increased proliferation and drug resistance.

2949 The regulatory effect of microRNAs on STAT signaling in malignant mesothelioma
Lisa Arzt1, Hannelore Kothmaier1, Franz Quehenberger2, Iris Hallwedd1, Helmut H. Popper1. 

Background: A major pathology of malignant pleural mesothelioma (MPM) is the uncontrolled cell proliferation and the fast local spreading with rare metastasis. Therefore the inhibition of proliferation is a major therapeutic target. Proliferation of MM cells was linked to mitogen activated protein kinase (MAPK) activity. In this study we characterised the regulation of MAPK regulated CAA/ET/ENHancer binding proteins (C/EBP) and their role in MM cell proliferation. In five human MM cell lines, cytotoxic and nuclear protein expression was determined by immuno-blotting and immuno-chemistry in tissue sections. Transcription of C/EBPβ was downregulated by real time PCR and translation by a translation reporter assay. We observed a cell compartment specific expression pattern of p38-α, -β and -γ and MAPK in MM cells. Erk1/2 and p38 MAPK together up-regulated the expression of C/EBP-β and -γ, while C/EBP-α was not expressed. Compared to mesothelial cells C/EBP-α translation was reduced in MM, while the mRNA was constitutively expressed. MM cells expressed a relative high level of the C/EBP-α translation suppressor calreticulin, while eIF4E was not significantly modified. Cell proliferation was inhibited by either the blockade of Erk/2, or p38-γ and -α MAPK, or C/EBP-β. Transfection with a C/EBP-α vector reduced proliferation and increased the MM cell’s sensitivity to steroids. Our data implies that in human MM cells an epigenetic mechanism deregulates the translation control of the cell differentiation factor C/EBP-α which leads to increased proliferation and drug resistance.

2950 Epithelial-to-mesenchymal transition in malignant mesothelioma
Alicia Diaz-Baquero1, Beatriz Romero Romero 1, Lourdes Gomez-Izquierdo2, Rainiero Avila Polo1, Jose Martin-Juan1, Francisco Rodriguez-Panadero1, 1U.M.E. Hospital de Reina Sofia, H.U.U. Virgen del Rocío, Sevilla, Spain; 2UGC Intermunicipial de Anatomia Patológica, H.U.U. Virgen del Rocío, Sevilla, Spain; 3Instituto de Biomedicina (Ibiis), H.U.U. Virgen del Rocío, Sevilla, Spain

Epithelial-to-mesenchymal transition EMT is a molecular-cellular process actiuated during embryonic development and tissue remodelling, by which epithelial cells lose their polarity and cell contacts, acquire the expression of mesenchymal markers and manifest a migratory phenotype. The progressive loss of E-cadherin is coupled with expression of non-epithelial cadherins, process known as “cadherin switching”. As tumours often mimic embryonic development, it has been postulated that EMT represents a transient event in carcinomas progression. Malignant Mesothelioma MM could represent an EMT in vivo model, because tumor cells can exhibit epithelial, sarcomatous and biphasic differentiation. Forty five patients with MM were investigated by immunohistochemical expression of cadherins E-cadherin, β-catenin, SPARC and vimentin in two tissue microarrays. Protein expression was scored from 0 to 3 in tumour and stroma. Data were correlated with histologic patterns, thorascopic findings and survival. E-P cadherins expression was observed in 79,3% of epithelial MM without evidence in mesenchymal component of mixed and sarcomatous types. N-1 cadherins were detected in 20,6%, 29,4% and 17,6% of these histotypes, respectively. The mesenchymal markers were detected in 100% of sarcomatous and mixed MM and in a many samples of epithelial group. Immunohistochemical expression of mesothelial marker E-cadherin was detected in samples in 20,6%, 29,4% and 17,6% of mesothelial samples. The mesothelial marker expressed in 100% of sarcomatous MM and in 52,3% of treated MM. There were 30 men and 14 women. The median age was 58 years (range, 34-76). Most patients had a PS ≤ 1 (82%) and an epithelial histologic subtype (91%). The median time to progression (TTP) after first line chemotherapy was 6,1 months. The SLC was achieved in 21 patients (with a relapse more than 3 months), and a new regime in 20 patients (gemcitabine alone or with oxaliplatin). The other 3 patients were enrolled in a phase I study. According to RECIST criteria, a partial response was observed in 7 patients and 9 patients had stable disease after SLC. The median TTP after SLC was 3,8 months. The median survival was 12,2 months (range: 2 to 72 months). Four of these 44 patients then received third-line (4,8%) and two received fourth-line therapy (2,4%). Conclusions: Our experience suggests the feasibility of giving SLC to patients with MPM who are healthy at the time of disease progression. The optimal treatment has not been defined to date and prospective trials are needed in this setting.

2952 Multimodality treatment of malignant pleural mesothelioma
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There is no widely accepted standard of care for patients with malignant pleural mesothelioma (MPM). Multimodality treatment protocol should be the standard approach in suitable patients and performed as a part of a trial: Biopsy proven MPM of non-sarcomatoid cell type, T1-3, N0-1, M0, patient fit for extrapleural pneumonectomy (EPP), neo-/adjuvant chemotherapy, and radical hemithoracic irradiation. In this study we evaluated the outcome of our patients with MPM who were treated by multimodality schedule including EPP, radical hemithoracic irradiation, and cisplatin-pemetrexed/gemcitabine chemotherapy regime. A total of 29 patients who consecutively underwent multimodality treatment schedule, 15 men, 14 women, were included. Of the patients 24 had epithelial cell type, 5 were mixed. 12 patients had stage 1 disease, 6 had II, 10 had III, 1 had IV (after surgery). Perioperative mortality (in 1 month) was 14% (4/28), mortality during multimodal therapy schedule was 18% (5/28). Patients completed multimodal Schedule were 19 (68%). Of the 19 patients completed multi-modality treatment, 11 died, 8 are alive.
For all patients, 28 cases, median survival was 19 months. For 19 cases completed multimodality treatment schedule, MS was 41 months. For the 12 patients who were on the second line treatment, median survival was 7 months. For 5 patients who were on the third line treatment, median survival was 7 months. For 2 patients who were on the fourth line treatment, median survival was 7 months. In total, 12 patients completed multimodality treatment schedule, median survival was 43 months. For the remaining 22 patients who did not complete the multimodality treatment schedule, median survival was 7 months. In total, 24 patients died during the follow-up period. The median survival for selected cases was 43 months. The ten-year trend in the prevalence of chronic cough and phlegm among young adults in Italy

The presence of chronic cough and phlegm (on most days for a minimum of 3 months a year and for at least 2 successive years) identifies a subgroup of subjects with a high risk of developing COPD, independently of smoking habits. We sought to evaluate the ten-year trend in the prevalence of these symptoms among young adults in Italy in 1998/2000, a screening questionnaire was mailed up to 3 times to general population samples of 20-44 year-old subjects, and eventually given over the phone to the remaining non-responders, in the Italian Study on Asthma in Young Adults (ISAYA) (9 centres; response rate = 72.7%). The same procedure was repeated in the Gene Environment Interactions in Respiratory Diseases (GEIRD) study in 2007/2010 (7 centres; response rate = 57.2%).

In 4 centres (Pavia, Sassari, Turin, Verona) involved in both the studies, the adjusted percentage* of chronic smokers has decreased (from 34.3% to 27.4%; p<0.001) during the past decade. The adjusted prevalence* of chronic cough and phlegm (with the 95%CI) is reported in this table:

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>75% (71.7-79)</td>
<td>91% (82.10-10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Past smokers</td>
<td>11.2% (10.6-11.9)</td>
<td>10.4% (9.9-10.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Current smokers</td>
<td>19.3% (18.4-20.2)</td>
<td>21.2% (18.4-23.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Total</td>
<td>12.4% (11.9-12.8)</td>
<td>12.6% (11.5-13.9)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Adjusted for centre, type of contact (telephone vs mail), cumulative response rate, season of response, sex, age.

The overall prevalence of chronic cough and phlegm has not changed during the past decade among young adults in Italy, but a decrease is expected due to the observed reduction in the percentage of current smokers. The increase in the prevalence among non-smokers deserves further investigation.
Costs of COPD by disease severity
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Background: Chronic obstructive pulmonary disease (COPD) is one of the most common chronic and disabling diseases worldwide, and the societal costs are high.

Aim: To estimate the societal costs of COPD in Sweden and to examine the relationship between disease severity and costs.

Methods: The study sample was identified in earlier clinical examinations of general population cohorts within the OLIN (Obstructive Lung Disease in Northern Sweden) studies. The cohort consisted initially of 993 subjects fulfilling COPD spirometric criteria (GOLD). In 2009-2010, telephone interviews on resource utilization were made to a sample of 244 subjects, stratified by disease severity. Interviews were performed quarterly to minimize the risk of recall bias. A non-parametric Mann-Whitney U-test was used to test cost differences between groups; p-values adjusted by Bonferroni correction. Unit costs from 2010 were applied.

Results: A highly significant relationship was found between disease severity and costs. The mean annual total cost per patient in relation to disease severity (GOLD) was: stage I 4,811; II 5,665, III 7,068; and IV 20,665. Direct costs were higher than direct costs in all severity stages. For direct costs, main cost drivers were hospitalizations in stage III and IV, and drugs in stage I and II respectively. The main cost driver in indirect costs was productivity loss due to early retirement, except in stage I where the driver was sick-leave. In comparison with a similar study performed in 1999 a numerical increase in mean annual total costs per patient was observed (ns).

Conclusions: The results indicate that the societal costs of COPD in Sweden are substantial, and the costs increase considerably by disease severity.

2958
Associations between quantitative computed tomography (qCT) measures of emphysema and mortality
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Background: Knowledge is limited regarding associations between qCT measures of emphysema and mortality.

Aims: To examine 6-year mortality (all-cause and chronic lower airway diseases (ICD-10 codes J40-47) in relation to qCT measures of emphysema.

Methods: In the Norwegian GenKOLS study 2003-05, 947 ever-smokers (49% with COPD) aged 40-85 years performed spirometry and qCT examination. Lung inflation level was obtained by dividing CT measured lung volume by predicted TLC. CT emphysema was estimated using % of lung voxels with X-ray attenuation values less than -950 Hounsfield units (% low-attenuation areas (LAA)), expressed as %LAA quintile. Mortality data from 2003-09 were gathered from the Norwegian Cause of Death Registry. Gender-stratified Cox proportional hazards were modelled, adjusting for FEV1, COPD status, age, BMI, smoking, inflation level.

Results: Both all-cause (n=106) and chronic lower airway diseases mortality (n=31) increased with %LAA: from 3% and 0.5% in the lowest quintile to 32% and 9.6% in the highest quintile respectively. The main cost driver in indirect costs was productivity loss due to early retirement, except in stage I where the driver was sick-leave. In comparison with a similar study performed in 1999 a numerical increase in mean annual total costs per patient was observed (ns).

Conclusions: The results indicate that the societal costs of COPD in Sweden are substantial, and the costs increase considerably by disease severity.

2959
Impact of comorbidities on survival of patients with COPD according to GOLD stages
Zagazeta Jorge1, Cabrera Carlos2, Divo Miguel2, Cote Claudia2, Juan De Torres1, Josue Maria1, Ciro Casanova1, Victor Pinto-Plata1, Santiago Carriazo1, Maria Sanchez-Carpintero1, Javier Zulueta1,2,3,4,5,6,7,6,8,9,10,11, 1Pulmonary Medicine, Clinica Universidad de Navarra, Pamplona, Navarra, Spain; 2Pulmonary Medicine, Hospital Universitario Don Gran Canaria Dr. Negrín, Las Palmas de G.C., Canarias, Spain; 3Pulmonary and Critical Care, Brigham and Women’s Hospital, Boston, MA, United States; 4Pulmonary and Critical Care, Bay Pines Veterans Affairs Medical Center, Bay Pines, FL, United States; 5Pulmonary Medicine, Hospital Miguel Servet, Zaragoza, Spain; 6Pulmonary Medicine, Hospital Nuestra Senora de la Candelaria, Tenerife, Spain

Introduction: In COPD patients the impact of comorbidities on patient’s outcomes is gaining interest. The aim of our study is to describe the role of comorbidities on mortality according to COPD GOLD stages.

Methods: We enrolled and followed 1664 patients from the BODE cohort over 10 years in five tertiary centers in the USA and Spain. Demographics, anthropometrics, physiological, comorbidities and survival with cause of death were recorded systematically. Patients were grouped according to GOLD stages I-II, III and IV. Tukey’s test was used to compare means among groups. A multivariate analysis was used to select those comorbidities associated with mortality. The effect of comorbidities over survival time was explored using Cox proportional hazard.

Results: Groups characteristics and differences are shown in Table 1. GOLD IV subjects were significantly younger, had fewer comorbidities and higher mortality. Furthermore comorbidities did not influence mortality in these subject and they died mainly from COPD (Table 2 and 3).

2960
Glitazones are associated with reduced risk of COPD exacerbations and mortality among patients with diabetes
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Introduction: Moderators of systemic inflammation may reduce risk of exacerbations among patients with COPD. Glitazones, used in the treatment of diabetes, also have anti-inflammatory properties. We sought to assess whether glitazones were associated with a decreased risk of COPD exacerbations and mortality.

Study design: We performed a cohort study between 10/2005-09/2006 of all US veterans who received an oral antihyperglycemic medication (sulfonylureas, biguanides, or glitazones) on more than one occasion. Our outcome measures included outpatient COPD exacerbations, hospitalization for COPD, and all cause mortality. Our primary exposure was glitazone use compared to sulfonylureas and/or biguanides. We used GEE to estimate the effect of glitazones and to adjust for potential confounding factors.

Results: We identified 600,366 patients. Adjustment for age, sociodemographic characteristics, comorbidity, and markers of COPD severity had minimal effects on the point estimates. In comparison to either a sulfonylurea or biguanide, glitazones were associated with a significantly reduced risk of outpatient COPD exacerbation (Adjusted relative likelihood (Adj-RL), 95%CI: 0.82 (0.69-0.97)) and all cause mortality. Our primary exposure was glitazone use compared to sulfonylureas and/or biguanides.

Conclusion: Glitazones were associated with a significant reduction in COPD exacerbations and all cause mortality. We hypothesize that this association may be mediated through the anti-inflammatory properties of glitazones.
324. Comorbidities and management in primary care

2961 Association of comorbidity and mortality in COPD
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2School of Health and Medical Sciences, Orebro University, Orebro, Sweden; 
3Department of Respiratory Medicine, Orebro University Hospital, Orebro, Sweden; 
4Department of Medical Sciences, Respiratory Medicine & Allergology, 
Uppsala University, Uppsala, Sweden

Introduction: The aim of this study was to investigate the association of comor- 
bdity and mortality in patients with COPD and those with all cause mortality.

Methods: A total of 1548 patients with a diagnosis of COPD were randomly 
selected from 56 primary care and 14 secondary care centres in Sweden. The 
response rate was 75%. Information was collected using questionnaires in 2005 
and record review for the period of 2000-2003. The Swedish Board of Health and 
Welfare provided mortality data. Lung function and history of comorbidities were 
obtained from the patients’ records. This analyses included patients with available 
spirometric data. Cox’s proportional hazards model was used to estimate the hazard 
ratio.

Results: A total of 552 patients (aged 34-75) were included in the study, 43% 
men (mean age 65) and 57% women (mean age 62). Of all, 27% were current 
smokers and mean FEV1 (percent of predicted) was 58. Over five years, in to- 
tal 120 patients (22%) died, 13% in primary care and 33% in secondary care. 
Mortality was significantly higher in patients with ischemic heart disease/cardiac 
hospitalization, with hazard ratio 1.91 (95%CI 1.30-2.80), with hypertension, hazard ratio 1.83 (95%CI 1.22-2.75) and with underweight (BMI <20), hazard ratio 1.74 (95%CI 1.12-2.70) after adjustments for age, sex, smoking, education, level of care and lung function. There was no significant difference in mortality for patients with 
diabetes or depression.

Conclusion: Heart disease, hypertension and underweight were in study associated 
with higher mortality in COPD patients.

2962 Do patients suffering from heart failure (HF) and chronic obstructive 
pulmonary disease (COPD) tolerate beta blocker (BB) treatment?
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Anthony Jennings1, Juan Raurà Siles1, Francisco Ruiz2, 1Cardiología, Hospital 
Costa del Sol, Marbella, Málaga, Spain; 2Cardiología, Hospital Hospitopend, 
Estepona, Málaga, Spain

Justification and objectives: In clinical practice the use of BB in patients with 
COPD is frequently avoided due to the risk of their inducing bronchospasm. 
Nevertheless, cardioselective BB use under strict monitoring may be well tolerated 
by and beneficial for many patients with HF and COPD.

Methods: We analyzed our experience with patients suffering from both HF and 
COPD who were given outpatient BB treatment. Those suffering from severe 
COPD were excluded.

Results: The group to be treated was made of 43 patients aged 63 ± 8 with an aver- 
age fraction ejection of 29, 2±6%, 60% of them of ischemic heart disease etiology. 
Patients were separated in two groups: Group A, patients with airways obstruc- 
tion and significant reversibility after bronchodilator test (FEV1 < 80% predicted) and 
FEV1/FVC <0.7. Group B patients with confirmed fixed airways obstruction mild or moderate 
(FEV1 75.4±3.75%, FEV1/FVC 0.60±0.51). All patients started treatment with 
BB in low doses, which were gradually increased up to maximum tolerated ones, 
no acute episodes of respiratory failure being shown in a 11 ±3 months follow- 
care period. The BB dosage had to be limited before reaching optimal levels in 
just 5 patients due to worsening dyspnea. According to NYHA classification, 
their functional status improved after the use of these drugs (p <0.01).

Conclusion: The use of BB under specialized cardiologist monitoring can be 
beneficial for patients suffering from both HF and mild-moderate COPD. The 
consequences of depriving patients of this treatment could be more harmful than 
the possible respiratory complications that might set in after its administration.

2963 Dysfunctional breathing in asthma patients
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Dysfunctional breathing (DB) coexisting with BA presents difficulties for clin- 
icians. Criteria to distinguish these conditions are not defined. This study was 
aimed at investigating DB in patients with or without BA.

Methods: This was a single-center cross-sectional study. We used the language of 
dyspnea, HADS scale, the Niknem questionaire, spirometry, capnometry, and 
blood gas analysis.

Results: 29 BA patients and 7 DB patients participated in the study. Of BA pa- 
tients, 5 had clinical signs of DB (BA+DB group). Patients with DB and BA+DB 
described their dyspnea as "I am gasping for breath" (28.6% and 40%, 
respectively, vs 4.2% of "pure" BA) and "My breathing requires more concentration" 
(42.9% and 42% vs 10.3%, respectively). Only 1 BA patient (4%) described 
expiratory difficulties. FEV1 was 2.35±0.95 L in "pure" BA; 2.08±0.62 L in 
BA+DB and 3.13±0.9 L in DB group (p<0.05). Anxiety, hyperventilation and 
blood hypocapnia prevailed in BA+DB group; median HADS-A scores were 12.0 
(11.0 – 13.0), 9.0 (4.0 – 11.0) and 7.0 (3.0 – 8.0). The Niknem scores were 30.0 
(27.0 – 31.0); 21.0 (15.0 – 32.0) and 14.5 (8.0 – 25.5) in BA+DB, DB and "pure" 
BA groups, respectively.

Anxiety and hyperventilation in asthma patients with and without dysfunctional breathing

<table>
<thead>
<tr>
<th>“Pure” BA group</th>
<th>BA + DB group</th>
<th>DB group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS-A &gt; 8</td>
<td>20.8</td>
<td>86.0</td>
</tr>
<tr>
<td>Niknem &gt; 23</td>
<td>33.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Alveolar hypocapnia</td>
<td>11.5</td>
<td>20.0</td>
</tr>
<tr>
<td>Arterial hypocapnia</td>
<td>12.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Data are given in % of patients. *p<0.05 vs “Pure” BA group.

Conclusion: Most BA patients perceive inspiratory dyspnea but its quality de- 
pends on coexisting DB. Alveolar and arterial CO2 are not indicative in up to 75% 
of patients with DB. Therefore, distinguishing DB from BA should be primarily 
based on verbal descriptions of dyspnea.

2964 COPD disease severity stratification obtained by electronic review of 
routinely collected primary care data
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Population Health Sciences, University of Edinburgh, Edinburgh, United 
Kingdom; 3Clinical Review Services, Optimum Patient Care, Norwich, United 
Kingdom; 4NHS Improvement: Lung, NHS, Leicester, United Kingdom; 2GP, 
Armed Services, Plymouth, United Kingdom; 2General Practice and Primary Care, 
University of Aberdeen, Aberdeen, United Kingdom

In COPD there are as yet many unknowns with regards to quantification by 
severity strata and identification of high risk patients. As part of an incentivised 
COPD improvement scheme, the clinical notes of 310,924 patients were reviewed 
electronically. COPD severity was categorised by lung function and the DOSE 
index to ascertain their need for medical intervention based on health status and 
exacerbation history.

Results: 4214 had COPD as a coded diagnosis (prevalence 1.4%) of which 609 
(14.5%) did not conform to NICE spirometric criteria for COPD (FEV1<80% 
predicted) and 525 were of unknown severity. Further stratification employing the 
multicomponent DOSE index with a cut off score of 4 revealed 177 high risk 
patients, suitable for active case management.

Stratification based on % predicted FEV1

<table>
<thead>
<tr>
<th>Severity</th>
<th>% of those with COPD</th>
<th>Number (3060)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>14.2</td>
<td>438</td>
</tr>
<tr>
<td>Moderate</td>
<td>49.8</td>
<td>1534</td>
</tr>
<tr>
<td>Severe</td>
<td>28.8</td>
<td>887</td>
</tr>
<tr>
<td>Very</td>
<td>7.2</td>
<td>221</td>
</tr>
</tbody>
</table>

DOSE: patients counted twice.

Current individual management was assessed comparing status and treatment 
against NICE COPD guidelines. Recommendations: 23.7% update spirometry, 
17.8% oxygen saturation assessment 38.8% refer for pulmonary rehabilitation. 
Pharmacologically, 56.1% were receiving oxygen therapy;11.2% were receiving 
no therapy.

Discussion: The use of electronic record review at practice level facilitates quantifi- 
cation, stratification and classification of patients by disease severity. This should 
facilitate individualised patient management by permitting therapy mapping and 
identifying patients at most risk of exacerbation/hospitalisation who merit more 
frequent review. At a population level, healthcare planning is facilitated.

2965 Integration of COPD management across primary and secondary care: 
Feasibility and impact
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Introduction: Integration of COPD treatment across primary and secondary care

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aim to maximize resources, reduce waste, and optimize care. We evaluated a service innovation in COPD across two hospitals and two primary care trusts (PCTs) between 2008 and 2011.

**Methods:** Five enhanced services: hospital-based admission-response; integrated pulmonary rehabilitation (PR); intermediate care COPD service; bespoke electronic COPD clinical record; 24/7 emergency telephone support service. The evaluation used routinely collected data to assess COPD admissions, primary care COPD prescribing, contacts in the new services, interventions and outcomes in the intermediate care service, and impact of 24/7 telephone support, and compared outcomes to two adjacent PCTs.

**Results:** 6068 patients with COPD were identified in a population of 511,000 served by 98 practices. 2308 (38%) patients were referred to PR, an increase of 35%. 1100 patients were seen by the admission response service, 1230 in the intermediate care service, and 453 were registered to use the 24/7 emergency telephone line. Average admissions were 980/year, stable during the project, and did not differ from admissions in 2.75 years before the project. Steady increase in prescribing of inotropium and of inhaledcombination long-acting bronchodilators and corticosteroids. No differences in numbers of COPD admissions or prescribing rates compared to two adjacent PCTs over the same period. No differences in admission compared to 29 London PCTs.

**Conclusions:** No impact of integrated COPD care was seen despite substantial numbers of patients and practices taking part. Rising prescriptions of COPD drugs were not reflected in a fall in admissions.

### 2966

**Comorbidity at time of COPD diagnosis**

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**Rationale:** Comorbidities can potentiate the morbidity of chronic obstructive pulmonary disease (COPD), and vice versa. Patients with COPD often die as a result of comorbidities.

**Objectives:** Evaluate prevalence of comorbidities at COPD diagnosis in real-world patients over a 10-year period.

**Methods:** Retrospective study using data from the United Kingdom’s General Practice and Optimum Patient Care research databases. Eligible patients were ≥40 yrs; received first COPD diagnostic code between 1990–2009; prescribed ≥2 COPD therapies in the year following diagnosis; had ≥2 yrs clinical data prior to diagnosis. Prevalence of asthma, ischaemic heart disease (IHD), gastroesophageal reflux disease (GERD) and diabetes mellitus (DM) were evaluated using diagnostic codes and (for GERD and DM) prescribing records before COPD diagnosis.

**Results:** Of 153,720 eligible patients: 52.6% male, diagnosed with COPD at median (IQR) age 68 (60–75) yrs. Over the period, asthma was recorded in 53.3% of patients, falling from 71.1% in 1990 to 29.7% by 2008. In the 2 yrs prior to their COPD diagnosis, 7.7% of patients consulted for IBD and 18.5% consulted, or received prescriptions, for GERD and 9.6% for DM. The percentage of patients consulting for comorbidities prior to COPD diagnosis increased over the study period. IBD from 6.5% in 1990 to 11.5% in 2009; GERD from 1.5–8.4% and DM from 4.4–12.5%.

**Conclusions:** These data confirm the presence of comorbidities in a substantial proportion of the UK COPD population. Trends over the study period suggest better differentiation of asthma and COPD diagnoses in recent years. The increasing prevalence of comorbidities may indicate increased awareness of comorbidities or improved diagnosis of COPD in patients treated for comorbidities.

### 2967

**Short-term outcomes in community heart failure patients with chronic obstructive pulmonary disease**

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**Aims:** Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are common co-morbidities. The combination presents diagnostic challenges and has been linked with worse prognosis in patients admitted to hospital. There is hardly any prognostic data in patients with both co-morbidities in the community.

**Methods and results:** We evaluated 783 patients (27.2%) with left ventricular systolic dysfunction under the care of a regional nurse-led community heart failure team between June 2007 - June 2010. 101 patients (12.9%) also had a diagnosis of COPD. 94% of patients were on loop diuretics; 83% on ACE inhibitors, 74% on β-blockers; 9.6% were on bronchodilators and 43% on aldosterone antagonists. Mean age of the patients was 77.9±5.7 years; Mean follow-up was 28±2.9 months. β-blocker utilization was markedly lower in patients receiving bronchodilators compared to those without (overall 24.4% vs 81%; P<0.0001). 24 month survival was 95% in patients with HF alone and 89% in those with both co-morbidities (P<0.001). The presence of COPD was associated with increased HF hospitalizations (HR 1.56 (1.4–2.1; P<0.001) and major adverse cardiovascular events [HR 1.23 (1.03–1.75); P<0.001].

**Conclusions:** COPD is a common co-morbidity in ambulatory HF patients in the community and is a powerful predictor of worsening HF. It does not however appear to affect short-term mortality in ambulatory HF patients.

### 325. Noninvasive ventilation on the intensive care unit: from novel application to end of life issues

**3268**

**Noninvasive mechanical ventilation in patients with acute respiratory failure due to H1N1 infection**

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We evaluated the clinical outcomes of consecutive patients positive for H1N1 and admitted to 6 Intensive Care Units in Italy for severe Acute Respiratory Failure and requiring non-invasive mechanical ventilation (NIV). 29/54 (54%) patients admitted to the ICUs needed immediate intubation for gasping, coma or respiratory arrest. The remaining 25 patients (mean age 49.8±12) underwent an NIV trial as a first line treatment using the helmet (n.19 patients) or a total face mask (n.6). Arterial Blood Gases (ABGs) at enrolment were: pH=7.41±0.02, PaO2/FiO2=117±64 and PaCO2=40±4.8. At the first ABGs control (between 30’ and 90’PaO2/FiO2 significantly (p<0.001) improved to 187±43 with a concomitant decrease in PaCO2 to 36±4.9. Mean duration of NIV was 49.8±33 hrs. 10/25 (40%) of the patients required intubation after 20.3 hrs. Overall mortality rate was 7/25 (28%), with all the deaths occurring in the NIV failure group. NIV failure had a lower PaO2/FiO2 at admission (78.6±21 vs 152.4±32 p<0.01, for NIV failure and success, respectively) and 5/7 patients had a known risk factor (i.e.hematological malignancies (n.2), previous solid organ transplant (n.1), multisystemic scorers (n.1) and CHF (n.1)). None of the operators were apparently contaminated by the virus. NIV may be safely used to treat patients with severe ARF due to H1N1 infections. The success rate was similar for that reported in the literature for ALI/ARDS patients.
in pandemic influenza A H1N1 pneumonia. However, other authors have recently reported some cases demonstrating the effectiveness of NIV in ARDS/ALI related to H1N1 pneumonia.

Aims and methods: The objective of this study is to describe the clinical characteristics of patients with diagnosis of Influenza A H1N1 pneumonia with ARDS/ALI with whom NIV has been effective. 75 patients affected by Influenza A H1N1 pneumonia with ARDS/ALI were treated by NIV. The outcomes of 10 historical control pts who received Standard Medical Treatment (SMT) alone (Group B).

Methods: Prospective analysis of the short-term outcomes of 10 NMD pts who were treated by NIV and AC immediately after extubation (Group A) and comparison with the outcomes of 10 historical control pts who received Standard Medical Treatment (SMT) alone (Group B).

Results: Significantly fewer pts who received the treatment protocol required reintubation and tracheostomy compared with those who received SMT (reintubation: 3 vs 10; tracheostomy: 3 vs 9; p=0.002 and 0.01, respectively). Pts in Group A remained for a shorter time in the ICU compared to Group B (7.8±3.9 vs 23.8±15.8 days; p=0.006).

Conclusions: Preventive application of NIV plus AC after extubation provides an important advantage to NMD pts by averting the need for reintubation or tracheostomy, and shortening their stay in the ICU.

2972

Patients sleep under noninvasive ventilation (NIV) in the intensive care unit (ICU)?

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Rationale: Whether patients receiving NIV are really sleeping in the ICU, and whether sleep occurs during the NIV sessions is unknown. In addition the ventilator used may influence patient-ventilator synchronization (1) and cause sleep disruption (2).

Objectives: 1. To analyze sleep quality and quantity in ICU patients receiving NIV for a acute hypopneic respiratory failure (AHRF). 2. To compare sleep between two different types of ventilators (these results are not yet available).

Material and methods: Prospective study on consecutive ICU patients treated by IV therapy for AHRF on the 2nd to 4th day of admission patients were randomized to receive NIV with their current ICU ventilator or with a specific NIV ventilator (Respironics V60) and a polysomnographic study was conducted during a 17 hour period (1am to 8am).

Results: 14 patients included, 7 in each group, age 73±9, pH 7.28±0.07, PCO2 77±1.8 mmHg. Previous respiratory disease: COPD 39%, obesity hyperventilation/sleep apnea syndrome 43%. Time under NIV previous to inclusion 18±11 hours. Time under NIV during the study period 75.4±1 hours in 2 or 3 sessions.

During the study period patients slept 5.8±2 hours (42±2% stages i+2 38.6±2% stage 3. 12±2% REM) with a fragmentation index of 29±13 arousals and awakenings per hour of sleep. 76% of the total sleep time (4.5±1.3 hours) happened during the night period (11pm to 8am), and 80% took place under NIV.

Conclusions: In patients treated for AHRF in the ICU, sleep architecture is relatively preserved, with most of the sleep time occurring at night. NIV seems to favour sleep during the night period.


2973

Ethical issues in idiopathic pulmonary fibrosis with acute respiratory failure (IPF-AHF): An Italian survey

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Aims: To determine Italian Pulmonologist’s attitudes and behaviour towards diagnostic and therapeutic choices in competent IPF-AHF patients.

Methods: A web-site survey (30-items questionnaire) was sent to all the members of the Study Groups of Respiratory Intensive Care and Diffuse Lung Diseases of Italian Association of Italian Pulmonologists (January-March 2009).

Results: 248/370 (67%) physicians responded to the questionnaire (>60% over-fifties, male, Catholics). About 75% of respondents agreed on having anticipated directives and on eventu-

ally communicating bad news about IPF-AHF. >75% of respondents answered that any diagnostic (BAL and/or TBB) and therapeu-
tical choices (drugs, ventilation, palliative care) should be discussed with the patients and relatives. However, almost 50% of respondents reported to start ventilation and palliative care only in <25% of cases. BAL under NIV was recommended to eventually find the cause of ARF by half of respondents, while 77% reported to perform BAL and/or TBB in >25% of cases. More responders stated that NIV was not likely to improve survival (76.7% vs 10.0%) and to facilitate the communication with the relatives (50.7% vs 19.4%). 43.5% of the physicians did not agree on the concept of using NIV to reduce dyspnea and 40% on its use to gain time for end-of-life decisions. >60% of the
respondents considered to perform NIV and intubation when a reversible ARF cause is supposed. About 60% of the respondents used NIV and palliation in <25% of cases, while >90% of them intubated patients in <25% of cases. Conclusions: A discrepancy between attitudes and behaviour of Italian Pulmonologists emerged towards IPI-ARF issues.

2976

Does manual therapy provide additional benefit to breathing retraining in the management of dysfunctional breathing? A randomised controlled trial

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Introduction: Dysfunctional breathing (DB) is a respiratory disorder associated with significant patient morbidity. It is characterized by unexplained breathlessness and an abnormal breathing pattern, with combinations of erratic breathing, episodic breath holding and sighing, or hyperventilation. Treatment involves breathing retraining through respiratory physiotherapy. Recently, manual therapy has been used as a treatment component; but no evidence exists to validate its use. We sought to investigate the effects of manual therapy in addition to breathing retraining in patients with DB.

Methods: 60 subjects with primary DB were randomized into either breathing retraining (standard treatment; n=30) or breathing retraining plus manual therapy (intervention; n=30). Both groups received standardised respiratory physiotherapy.

Table 1. Analysis of primary and secondary outcomes

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Treatment Effect (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nijmegen score</td>
<td>2.8 (–1.1 to 6.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>BAD Anxiety</td>
<td>0.6 (–0.8 to 2.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>BAD Depression</td>
<td>0.3 (–0.6 to 1.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Breath hold</td>
<td>1.4 (–2.8 to 4.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.02 (–0.04 to 0.09)</td>
<td>0.45</td>
</tr>
<tr>
<td>FVC</td>
<td>0.01 (–0.09 to 0.1)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

DB education; breathing retraining; home regime; audio disc. Subjects in the intervention group received additional manual therapy.

Results: No significant difference was found between groups for the primary outcome Nijmegen score or any secondary outcome measures (Table 1).

Conclusion: Breathing retraining is the primary management for patients with DB. Our results suggest the additional use of manual therapy provides no further benefit and cannot be recommended in clinical practice.

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Efficacy of airway clearance therapy with different autonomy degrees in nonCF-BE patients: Randomized cross-over trial

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Airways clearance techniques are an important part of chronic treatment of non-cystic fibrosis bronchiectasis (nonCF-BE). Notwithstanding, the literature supporting their clinical use is still poor.

Aim: To evaluate effectiveness in mucus clearance and tolerance of 3 respiratory techniques with different autonomy degrees: ELTGOL (physiotherapist-administered), Autogenic drainage (self-administered) and a temporary positive expiratory pressure device, named Uniko.

Design: Randomized cross-over trial.

Population: Clinically stable adult nonCF-BE patients, sputum production ≥15ml/day.

Methods: Each technique is applied in 3 sessions on alternate days (1 week washout). Sputum was registered at the end session, after 1h and 24h.

Results: 7 patients were enrolled in the study (median age 69; mean FEV1 70%; 66%). AD obtained the major short-term sputum production (mean values: ELTGOL 7gr.; AD 15gr.; Uniko 7gr.). By contrast, Uniko and ELTGOL showed a higher sputum production at 24h (AD 9gr., Uniko 16gr., ELTGOL 17gr). The short-time sputum production slightly increased over time with ELTGOL (1st: 11gr.; 2nd: 13gr.; 3rd: 14gr.), while the 24h sputum production increased with Uniko (1st: 14gr.; 2nd: 17gr.; 3rd: 17gr.). AD was the favourite technique of 6 patients.

Conclusions: The 3 techniques were well tolerated and efficacious. AD was the most rapid in favouring expectoration. However, Uniko and ELTGOL were more effective at long-term, with an increasing trend for Uniko over time. The degree of patients’ autonomy for each technique, the compliance and personal preferences should be considered to select a treatment in order to individualize and optimize the respiratory therapy in nonCF-BE patients. Supported by MIR Italy.

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Nebulised 7% hypertonic saline improves health related quality of life in patients with non-cystic fibrosis bronchiectasis

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Introduction: Cough and sputum have a significant impact on quality of life (QoL) in non-cystic fibrosis bronchiectasis (NCFBx). Nebulised 7% hypertonic saline (HTS) has previously been shown to improve airway clearance in NCFBx, and we hypothesised that it would also improve QoL in such patients.

Method: Patients with NCFBx referred for HTS for over a 4 month period at Royal Brompton Hospital were included (N=22). Patients were assessed by the Leices- ter cough questionnaire (LCQ) as a marker for Health Related Quality of Life (HRQoL). Visual Analogue Scale for ease of clearance (VAS/EC) and FEV1 pre and post 1 month use of HTS Results are expressed as median and interquartile range and Wilcoxon-signed Rank tests were used to assess the impact of the therapy.

Results: N=22 (Males=7), median age 64yrs (32.81), FEV1, 1.59 (0.64-3.01). There was a significant improvement in LCQ 11.0 (9.2-14.7) to 16.7 (10.7-17.7) p<0.01 and VASE/EC 7 (5.5 - 8) to 4.7 (3.7) p<0.002. There was no significant change in FEV1 (p=0.32). 4 patients (18%) constituted on challenge test, and were not included in analysis. No other adverse effects of the therapy were seen.

Conclusion: In addition to confirming that HTS improves airway clearance, we demonstrated for the first time that HTS also improves HRQoL markers in patients with NCFBx. The minimal clinical significant difference in the LCQ is reported to be 1.5-3.7. There was therefore a statistically and clinically significant change in the total LCQ score, suggesting HRQoL significantly improved with one month use of HTS. Further trials with HTS are needed to assess whether these improvements are sustained long term in such patients.
Comparison of two physiotherapeutic methods in bronchiectasis: Active cycle breathing technique (ACBT) and oscillating physiotherapy device

Hamil Reza Khoddami Visheh, Fariba Gohbani, Masoomeh Masoudinia, Saeid Mahmoudian, Shahid Shafaghat, and Mohammadreza Rezaei

Aim: To evaluate the efficacy of mobilization and active cycle of breathing techniques (ACBT) following coronary artery bypass graft (CABG) surgery.

Material and methods: Fifty patients (35-75 years) with CABG were included in this randomized study. Twenty-five patients (18 males, 7 females) underwent mobilization and 25 patients (21 males, 4 females) were applied ACBT combined with mobilization. Demographic variables were recorded. Patients were evaluated using pulmonary function testing, 6-minute walk test (6MWt), and respiratory muscle strength.

Results: Five days after surgery, pulmonary function variables were similarly but significantly decreased in both groups as compared to preoperative values (p<0.05). No significant difference was found in 6MWt distance obtained before and after surgery, and no side effects during and after the study were observed. No significant difference was found in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) in both groups.

Conclusion: Functional capacity preserved after short-term ACBT or mobilization intervention after CABG surgery. Improvement in respiratory muscle strength was faster in ACBT group.

A randomized prospective cross-over study was performed in 16 patients with SRD under noninvasive mechanical ventilation (NIV). Patients with a median age of 51.5 (39.7-64.7) years that included 13 neuro muscular disorders (SRD), sleep events defined as obstructive or central apneas/hypopneas, and a mean AHI of 5.7±3.0 (1.1-16.9). All patients were included in the SRD group and were included in the study. The study was divided into two phases: Phase I: After the first night with a PEEP/EPAP of 0 cmH2O and the other night with a PEEP/EPAP of 8 cmH2O. Phase II: Two consecutive nights, they were randomly assigned to sleep one night with a PEEP/EPAP of 6 cmH2O and the other night with a PEEP/EPAP of 8 cmH2O.

Conclusion: The application of PEEP/EPAP did not show superiority in terms of sleep parameters and overall satisfaction (P>0.05). However, patients believed that they can do physiotherapy with RC-comet® method at home alone than ACBT method (25 vs. 15, P=0.022). Conclusion: Our findings showed that use of RC-comet® at home is preferred by most of the patients. Since this method was more acceptable and preferable than ACBT for home usage, we highly suggest use of such convenient methods.

Comparison of PEEP/EPAP during nocturnal noninvasive ventilation in patients with severe restrictive disorders: Physiological effects and tolerance in a randomized pilot study

Miguel Goncalves1, Joaquim Moreira 2, Luana Souto Barros 2, Patricia Dantas 2, João Carlos Winck 1

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Conclusions: Concentration of bronchoalveolar interleukin-1 beta was significantly higher in the children with positive and negative bacterial culture, respectively (p = 0.001). Bronchoalveolar interleukin-1 beta was significantly positively correlated with parameters of body composition and serum concentrations of leptin and adiponectin were significantly associated with higher estimates for Charlson index (RR 1.38; 95% CI 1.04 to 1.82, p=0.02) and APACHE II scale (RR 1.242; 95% CI 1.284 to 1.602, p=0.005). In convalescents the increased lung pattern on radiographs (39%), decreased lung diffusion capacity (45%), restrictive changes (15%) were the most frequent and long-lasting changes. 28% of patients having these changes applied for medical care within 6 months after being discharged.

Conclusion: The high score on Charlson index and APACHE II scale are risk factors for development of severe pneumonia in presence of influenza A (H1N1). Changes of ventilation functional tests associated with persistent disorders of pulmonary circulation remain for long time in 45% of patients undergoing pneumonia. This group of patients is of particular interest and requires further observation.

2987 Specialised palliative care is more than drugs – A retrospective study of ILD patients
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Background: Little is known about the palliative care needs of patients with Progressive Idiopathic Fibrotic Interstitial Lung Disease (PIF-ILD). As part of a study to develop a complex palliative intervention at the end of life, we retrospectively studied patients dying in 2 London Hospitals.

Aims: To assess the palliative care needs and management of PIF-ILD patients in 2 London ILD centres.

Methods: Patients’ records from Royal Brompton Hospital (RBH) and King’s College Hospital (KCH) were extracted to assess palliative care needs, use of palliative treatments and whether end of life preferences were documented and achieved.

Results: 45 PIF-ILD patients were identified (26 RBH,19 KCH). Patients at RBH were younger (37±18 years, median 30) compared to KCH’s older, more racially diverse population (70-99y, median 82y, 6/19 non-white).

All patients experienced breathlessness in their last year of life (42/45) and almost a third (17/45) patients had specialist palliative care team involvement. Nearly all patients (44/45 patients) were non-white. In 181 patients who died, 144 (79%) died in hospital (3.3 days from diagnosis to death) and 18/45 (39%) died at home (3.2 days from diagnosis to death).

Conclusion: Despite demographic variation, the patients experienced similar symptoms. There was use of standard pharmacological treatments with symptom related with bacterial burden in the alveoli, it may be a marker for progressive and ongoing inflammation in children who have not responded to CAP therapy.

2988 Community-acquired pneumonia in pediatric patients with connective tissue disorders: Manifestations and clinical course
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Objective: To assess the relationship between concentrations of bronchoalveolar cytokines and bacterial burden in children with CAP.

Method: 58 children were divided into two subgroups: referral (n=28), and treated (n=30) CAP. Bronchoalveolar lavage was performed in the most abnormal area on chest radiograph by fiberoptic bronchoscope. Bronchoalveolar lavage fluid was processed for quantitative bacterial culture. The concentrations of bronchoalveolar lavage cytokines (tumor necrosis factor-α, interleukin-1 beta, interleukin-6, interleukin-8, and interleukin-10) also were measured.

Results: Thirty-two patients had a positive bacterial culture (bronchoalveolar lavage > or = 10 colony-forming units/mL), and made up 70% of pathogens recovered at high concentrations. The concentrations of bronchoalveolar lavage interleukin-1 beta were 18.1±11.63 and 45.1±10.67 pg/mL, (mean ± s.e) in the children with positive and negative bacterial culture, respectively (p = 0.001). Bronchoalveolar lavage interleukin-1 beta was significantly higher in the children with a high bacterial burden (p = 0.001), with mixed bacterial infection (p < 0.001), and with CAP (p < 0.001), compared with values in patients without these features. The relationship between bacterial load and concentrations of bronchoalveolar lavage interleukin-1 beta was very strong in the children with referral CAP but was borderline in treated CAP.

Conclusions: Concentration of bronchoalveolar interleukin-1 beta was correlated with bacterial burden in the alveoli, it may be a marker for progressive and ongoing inflammation in children who have not responded to CAP therapy.
clinical course of community-acquired pneumonia (CAP) in pediatric patients that leads to diagnosis and therapeutic mistakes.

**Aims:** To study role of CTD in CAP clinical course in children.

**Methods:** 171 children aged 0.18 years with CTD and CAP were observed. CAP was clinically and radiographically diagnosed with detection of serum antibodies (IgG and IgM) against intracellular pathogens measured by enzyme-linked immunosorbent assay (ELISA) and PCR.

**Results:** Recurrent course of CAP (with 3 and more episodes in 5-year period of study) was in 106 (61.9%) patients and in all cases followed a viral respiratory infection. 156 (91.2%) children had abnormal perinatal history. Asthma (A) was diagnosed in 59 (34.5%) children. CAP caused by *Mycoplasma pneumonia* (Mp) was in 88 (51.5%) patients; by *Cytomegalovirus* (Cmv) and *Mp* – in 42 (24.5%); by *Chlamydia pneumoniae* (Cp) – in 18 (10.5%); by *Cp* and *Mp* – in 33 (13.5%) patients. 78% of patients with A, CTD and CAP and 53.6% of patients with CTD and CAP had pulmonary hypertension (PH). 76.4% of patients with recurrent CAP demonstrated radiographic and clinical evidence of pulmonary fibrosis (PF), 30.2% of them had A. 12.5% of children with A, recurrent CTD, recurrent CAP and PF had evidence of development of PC.

**Conclusions:** 1. Manifestations of CTD were in all children with CAP. 2. All patients with CTD and recurrent CAP had abnormal perinatal history. 3. High frequency of PH and PF was observed in patients with CTD and recurrent CAP. 4. 12.5% of children with A, recurrent CTD, CAP and PF had evidence of development of FC.

### P2989 Clinical features of a new hypersensitivity pneumonitis: Salami brusher’s disease

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**Internal Medicine and Pneumology, Fidighe di S. Camillo Clino, Cremona, Italy**

We observed 5 consecutive cases of hypersensitivity Pneumonitis (HP) in subjects working in a salami factory. The workers had to clean the mould growing on salami’s surface by using a wire brush. The working population was of 30 female subjects, 5 of them developed a HP (17%). Two were smokers (40%) and, other two were asthmatic. All patients presented with an acute clinical manifestation with cough, high fever, dyspnea and hypoxemia. One participant was admitted after a short period after exposure (240±60 minutes). Three of them presented at the emergency department and a chest x-ray showed and alveolar interstitial pneumonitis and were treated as a community acquired pneumonia. Skin prick test were positive for *Penicillium spp* in 3 cases and for *Cladosporium spp* and *Aspergillus spp* in other 2. The results of serum immunoglobulin (Ig) G and IgA antibodies against *Penicillium spp* were positive in 3 patients, 2 patients were positive to *Aspergillus Fumigatus*. Pulmonary function tests were performed a reduction in diffusing capacity in all 5 patients (60±15% of predicted). A bronchial hyperresponsiveness to methacholine was present in all the patients, the mean dose of methacholine causing a 20% fall in FEV1 was 3.63±4.70 mg/ml. RAL data showed a lymphocytosis 44.5±9.3%, CD4+ were 26.5±6.6%, CD8+ was 53.5±8.2%. Four patients had a complete recovery after changing work, and one was treated with oral steroids for increasing dyspnea and severe interstitial involvement. Salami’s brusher disease is a new type of HP; the prevalence is high in exposed subjects, and is common even in smokers. The disease has an acute clinical onset. The probable antigen is Penicillium, but *Cladosporium* and *Aspergillus* may play a key role.

### P2990 Predicting peak cycle work rate from the incremental shuttle walk test in COPD

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**Introduction:** The incremental shuttle walking test (ISWT) is used to assess physical activity and exercise performance in chronic lung disease: implications for rehabilitation.

**Methods:** 188 patients (94 men) performed an ISWT before a pulmonary rehabilitation program. Lung function, nutritional status and depression and anxiety symptoms were assessed.

**Results:** The mean (SD) age was 61.1 (10.2) years, FEV1 1.6 (0.54) L, RV/TLC ratio 59.0 (10.4%), BMI 26.0 (6.6), fat free mass index (FFMI) 18.9 (4.7), depression symptoms (HADS) 6.1 (4.2), anxiety symptoms (HADS) 6.9 (4.2). The ISWT distance was 209.6 (144.7) meters. The total variance explained by the model was 48.2%. R2 change: FEV1 (l) 28.5%, age 7.6%, depression symptoms 7.0%, BMI 3.8% and RV/TLC 1.3%. Sex, FFMI, smoking behavior and anxiety symptoms were not significant.

**Conclusions:** Prognostic variables for the ISWT are both physical (pulmonary and non-pulmonary) and psychological.

### P2993 Does breathlessness and leg discomfort indicate different exercise limiting mechanisms in COPD?

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**Introduction:** The last step in the complex cascade of patho-physiological mechanisms leading to exercise intolerance in COPD is the (prematurely) generation of symptoms, mainly dyspnea and leg discomfort. From a clinical perspective it is of
great interest whether these 2 distinct symptoms would point to different exercise limitation mechanisms.

Aim of the present study was to evaluate potentially different in dynamic hyperinflation and peripheral muscle strength between patients stopping exercise because of intolerable dyspnoea (D) or leg discomfort (L).

Methods: 496 patients with COPD (GOLD II-IV) performed a constant work rate cycle test at 75% of maximal power output till exhaustion. Ventilatory variables including inspiratory capacity (IC) were measured during this test. In addition, maximal peripheral muscle strength of the quadriceps (QF) was measured using a hand held dynamometer. Because the prevalence of exercise limiting factors related to FEV1, analysis of variance was performed for each GOLD class separately.

Results
Variable GOLD II (n=196) GOLD III (n=237) GOLD IV (n=61)
Stop reason D (n=95, 61%) D (n=9, 44.2%) D (n=26, 51.7%) D (n=35, 15%) D (n=89, 88%) D (n=9, 9%)
IC (L/min) 34.1 ± 10.8 32.5 ± 10.9 27.5 ± 10.4 15.9 ± 9.8
QF (kg) 29.3 ± 12.9 32.3 ± 12.3 30.5 ± 10.2 <0.05
ESWT (mmHg) 63.7 ± 13.7 62.5 ± 19.0 67.3 ± 16.5 <0.05
LCADL 31.7 ± 11.9 33.3 ± 12.4 39.6 ± 12.9 <0.05
HADa 8.6 ± 5.5 6.8 ± 3.9 8.1 ± 4.8 NS
HADb 8.8 ± 3.7 5.8 ± 3.7 7.9 ± 3.9 <0.05
% Weight bearing 25.9 ± 6.9 31.3 ± 6.7 18.8 ± 6.8 <0.05
% Moving 11.4 ± 4.1 13.1 ± 4.1 NS
Walking 4.5 ± 2.2 5.8 ± 1.9 3.8 ± 1.9 NS

Conclusions: Treadmill endurance test is more representative of daily activity, our aim was to determine the minimal important difference (MID) for treadmill test (TET) capable to detect improvement in functional capacity in patients with COPD after a 24 sessions PRP.

Material and methods: 100 COPD patients (mean age: 66.6±9.5 years old; FEV1: 1.1±0.4L) were enrolled. Patients performed a 6MWT and a symptom-limited TET at 90% of maximum grade achieved in an incremental test before and after the PRP. The St Georges Respiratory Questionnaire served as anchors for anchor-based MID estimates. Work rate (W), walked distance, endurance time and patients velocity in both tests were calculated.

Results: The TET minimal important difference found for W was 14.337 Joules or 37% increase and for endurance time an increase of 340 ± 77%.

Table 1. Changes and minimal important difference (MID) in 6 minute walk test (6MWT) and treadmill endurance test (TET) pre and post pulmonary rehabilitation program

<table>
<thead>
<tr>
<th>Variable</th>
<th>6MWT</th>
<th>Treadmill Endurance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-PR</td>
<td>Post-PR</td>
</tr>
<tr>
<td>Distance (m)</td>
<td>503.5</td>
<td>528.2</td>
</tr>
<tr>
<td>Time (s)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>1.40</td>
<td>1.50</td>
</tr>
<tr>
<td>Work (L)</td>
<td>35.14</td>
<td>36.69</td>
</tr>
<tr>
<td>MID Work (L)</td>
<td>Not found</td>
<td>Not found</td>
</tr>
<tr>
<td>MID Time (s)</td>
<td>Not found</td>
<td>Not found</td>
</tr>
</tbody>
</table>

Conclusion: Treadmill endurance test is more representative of changes in functional capacity than 6MWT in COPD patients after a PRP. In addition, work rate seemed to be a good variable to evaluate improvement in exercise capacity after a pulmonary rehabilitation program.

P2995
Predictors of six-minute walk distance at baseline and after three years in COPD patients
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Association between six-minute walk distance (6MWD) and COPD systemic markers overtime is unclear. The aim of this study was to verify the predictors of 6MWD at baseline and after three years in 53 COPD patients (66% male, age 63±49 years, FEV1=56±21%). The following evaluations were undertaken at baseline and after three years: body mass index (BMI), six-minute walk distance (6MWD), Modified Medical Research Council dyspnea scale (MMRC) and Interleukin-6 (IL-6). Information on exacerbations was not available at baseline and was collected during the study period. At baseline, FEV1, MMRC, BMI and IL-6 were included in a multiple linear regression analysis with the baseline 6MWD value as the dependent variable. After three years, we included the final values of the same variables with the final 6MWD value as the dependent outcome. In another model, we evaluated the influence of the number of exacerbations in the previous model. At baseline, FEV1 and IL-6 were selected as predictor of 6MWD (R2=0.44; p<0.001); however, after three years, only MMRC was selected as predictor of the walking distance (R2=0.54; p<0.001). The number of exacerbation did not influence 6MWD overtime. In conclusion, airflow limitation and inflammation are predictors of 6MWD at baseline. However, maintenance or improvement of exercise tolerance overtime in COPD patients is related to the control of dyspnea perception.

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P2996
The influence of O2 on exercise capacity (6-minute-walking-distance, 6MWD) in COPD
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We investigated the additional effect of supplemental oxygen on 6MWD in severe COPD-patients. The aim of the study was to find out if the response to nasal oxygen during 6-minute-walking-test (6MWT) depends on the level of exercise capacity.

To identify characteristics of patients with high oxygen response, we defined patients as “O2-Responder” if they increase their 6MWD by ≥35m due to oxygen supply

111 COPD-patients (age: 63.5±8.7, FEV1: 35.9±pred±11.6; F6O2=65.46) took part in a randomized, single-blinded, prospective study.

The patients underwent a 6MWT pretest followed by 2 6MWT either on 2L oxygen or on medical air (MA). After 3 week rehabilitation including resistance- and endurance-training both tests were repeated. We measured lung function before and after rehabilitation, SpO2, paO2, paCO2 and BORG-scale before and after every 6MWT.

The difference between 6MWDMA and 6MWDMAO2 (O2-response) was greater pre (A×17.6%) than post rehabilitation (A×3.25%). Separating patients in 2 groups, O2-responder was significantly higher in patients with 6MWD<349 m (p<0.05).

While Pulmonary Rehabilitation (PR) improves health status and exercise capacity in the short term, there is a lack of consistent evidence that daily physical activity increases after PR and if this is sustained.

17 stable COPD patients (mean age 67.7 (9.6y), FEV1 1.1 (0.4)l, 47 (16)% predicted) were assessed before and after 8 weeks PR and 6 mths later. The number of exacerbations during PR and if this is sustained.

While Pulmonary Rehabilitation (PR) improves health status and exercise capacity in the short term, there is a lack of consistent evidence that daily physical activity increases after PR and if this is sustained.

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While Pulmonary Rehabilitation (PR) improves health status and exercise capacity in the short term, there is a lack of consistent evidence that daily physical activity increases after PR and if this is sustained.
Although there is a correlation between the DASI and the ISWT, poor agreement does not necessarily lead to a change in daily physical activity. This is due to a lack in behavioural change and can subsequently lead to loss of an initial gain in exercise capacity. The results show that activity levels can be increased and the pattern can be changed. COPD patients show lower activity levels compared to controls and a less distributed pattern. First experiences with a telemedicine feedback intervention.

Conclusions: There're scarce studies evaluating long-term impact of exercise adherence after a respiratory rehabilitation program (RR) in Chronic Obstructive Pulmonary Disease (COPD) patients. To compare impact on BODE, mortality, health-related quality of life (HRQL) and health-resources consumption in two groups of COPD patient: intense physical activity (IPA) and low physical activity (LPA) at long-term. METHODS: COPD patients (GOLD definition) were followed up after a RR program completed (from 1997 to 2009). Patients were evaluated by BODE, HRQL (SGRO), pulmonary function, health-consumption and survival on 2009. Patients were classified according to García Aymerich questionnaire (Thorax 2006): IPA, LPA, IPA vs LPA. LONG-TERM IMPACT OF EXERCISE ADHERENCE
Quality of life represents a crucial aspect for the assessment of COPD patients. The level of daily activities is a determining factor and the degree of autonomy in movement is an important component that influences quality of life. Pedometry represents an alternative tool for estimating the degree of this activity.

Aims: To compare the values, obtained by pedometry of COPD patients (GOLD stage III and IV) with the values of healthy subjects from the Euroregion Banat.

Material and methods: We used pedometers to monitor 14 patients with COPD (not included in pulmonary rehabilitation) and 32 healthy subjects for a week, registering daily level and intensity of movement and detecting aerobic effort. Both groups had comparable demographic data and similar occupations.

Results: Healthy individuals showed a significantly higher average of steps over a full week compared with COPD patients (6497±1866 vs. 3992±295, p<0.05).

In both groups the number of steps was lower during the week-end compared with working days: 4754±2322 vs 7185±2396 steps for the control group, and 2135±697 steps vs 4736±175 steps in COPD patients (p<0.05). 52.77% of the normal subjects have made an aerobic effort at least one day in a week and only 13.88% performed a constant aerobic effort. Patients with COPD couldn’t perform an aerobic exercise at all.

Conclusions: We found a decrease in intensity of daily activity in healthy subjects, compared with data from literature, suggesting an increase of the sedentary style in general population. The degree of physical activity is significantly reduced in COPD compared with healthy people on both levels: aerobic and anaerobic effort.

For both groups, periods of week-end reveal the lowest activity level.

P3005 Does resistance training improve physical activity in patients with COPD? Lutzy Houchen1,2, Manoj Menon1, Samantha Harrison1, Carolyn Sandiland1, Michael Morgan1, Michael Steiner1, Sally Singh1,2, 1Institute for Lung Health, Glenfield Hospital, Leicester, United Kingdom; 2Faculty of Health & Life Sciences, Coventry University, Coventry, United Kingdom; 3Respiratory Medicine, University of Leicester, Leicester, United Kingdom

Introduction: Quadriceps (quads) weakness is a functional problem for patients (pts) with COPD. Resistance training (RT) can increase quads strength. The translation of increased strength to physical activity (PA) is less clear.

Aim: To determine if RT in isolation (outside of pulmonary rehabilitation) can increase PA in pts with COPD.

Method: PA was measured before and after an 8week RT course. RT was 5×30 bilateral knee extensions; 3 times/week on an isokinetic dynamometer (Cybex: speed = 180°/sec). Pts were enrolled in a trial of protein supplementation (PS) during RT. PS did not augment the benefits of RT & PA results are therefore pooled.

20 pts (mean [SD] age 69.2±9.4 yr, BMI 25.6±4.4, FEV1 48.8±13.3% predicted, 11 men) had PA measured using the DUEKI Activity Status Index (DASI (range 0-58.2)) & ActiTrac accelerometer (IM Systems: mean acceleration/min, average daily activity monitoring (Dynaport MiniMode, Roberts BV) were measured before and after rehabilitation.

Results: None of the patients was hospitalized in this rehabilitation period. There was no change in maximal exercise capacity (WRmax: 75.1±17 vs 82.6±21 Wtatt), but oxygen uptake (VO2:128±33 vs. 122±29±0.8 L/min; p<0.05) and lactate threshold (LAT: 0.68±0.18 vs. 0.88±0.20 mL/min; p<0.05) improved significantly. Patients with COPD were more active after rehabilitation (lying: 26±16 vs. 12±11%; locomotion: 7±4 vs. 14±3%; p<0.05). Energy expenditure was reduced at rest after rehabilitation (lying: 2263±1535 vs. 1273±6154 Wtatt, p<0.05), Step counts improved significantly (3257±2267 vs. 5688±2920, p<0.05). The time of locomotion modestly correlated with post-rehab WRmax (r=0.40, p<0.05) and FEV1 (%pred) (r=0.42, p<0.05).

Conclusion: Activity monitoring contributes to the complex evaluation of rehabilitative interventions. Compared to maximal exercise capacity, change in activity level proved to be more sensitive to detect improvement in the status of COPD patients in this pilot study.
in COPD as low levels are associated with hospital admissions and mortality. Objective measurements require motion sensors (e.g. SenseWear Arm-band, SWA), but several days are needed to obtain reliable data. We evaluated a previously unstudied tool in COPD, the Stanford Seven-Day Physical Activity Recall questionnaire (PAR), as a screening test for physical inactivity. As a control, three self-completed PA questionnaires were simultaneously evaluated.

Methods: 45 COPD patients were the SWA for 7 days. Patients, blinded to the armband output, then completed the PAR and 3 other questionnaires in randomised order. Spearman rank correlation and ROC curves were used to assess the relationship between PA questionnaires output and SWA-derived physical activity indices, and the ability of the questionnaires to predict very inactive COPD patients.

Results: With the PAR, total energy expenditure (r=0.83, p < 0.001), physical activity level (r=0.52, p < 0.001) and time spent in at least moderate physical activity (r=0.54, p < 0.001) correlated significantly with equivalent data from SWA. No relationship was seen between the other questionnaires’ output and any SWA-derived PA index. The PAR compared favourably with the other questionnaires in predicting very inactive COPD patients with an area under the curve of 0.79 (95% CI 0.63–0.94). A PAR-derived PAL < 1.40 had a sensitivity of 0.65 and a specificity of 0.89 in predicting very inactive COPD patients.

Conclusion: The PAR is a useful screening tool to predict physical inactivity in COPD patients.

P3007
Hypoxia induces differential acute and chronic adaptations in regulation of skeletal muscle protein turnover
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Hypoxia may be a trigger of skeletal muscle atrophy in acute and chronic respiratory disease. To test this hypothesis, short- and long-term regulation of muscle mass in response to normoxic or hypoxic conditions was investigated in mice.

During 48h, O2– levels were reduced stepwise to 8%, which was maintained for 21 days. Food intake was monitored daily and mice were sacrificed at days 4 and 21.

mRNA and protein expression levels were determined in gastrocnemius muscle.

Food intake was affected during short- (day 4: -50%) and long-term (d21: -20%) hypoxia. Compared to normoxia, gastrocnemius muscle weight decreased (d4: -11%, d21: -23%). The reduced food intake was partially responsible for this effect. Hypoxia increased expression of Atf4 (d4: +52%, d21: +31%) and Gadd45 (d4: +148%, d21: +73%) indicative for acute and chronic ER stress signalisation. Protein synthesis regulation was differentially affected by short- and long-term hypoxia (p=0.21 and d21: -23%, p<0.01, respectively). Atrogin–1 as proteasomal protein degradation marker was activated during acute and chronic hypoxia (d4: +128%, d21: +60%), whereas MuRF1 only at day 4 (d4: +102%, d21: ns) and was explained by reduced food intake. Short- and long-term hypoxia induced markers of lysosomal protein degradation Bnip3 (d4: +95%, d21: +74%) and Lc3 (d4: +18%, d21: +26%) which could be attributed in part to the reduced food intake.

In conclusion, these data suggest that acute adaptation of muscle mass to hypoxia reflects an increased protein degradation whereas chronic adaptation may involve increased protein turnover.

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329. Role of infection in exacerbations of COPD

P3008
Human metapneumovirus involved in acute exacerbations in COPD patients?
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Introduction: COPD is characterized by the occurrence of acute exacerbations (AE) which may be caused by several factors, including infections. Human metapneumovirus (hMPV) is an important cause of severe respiratory tract infections in young children, the elderly and immunocompromised subjects. This study evaluates the presence of hMPV, and other respiratory viruses in stable sputum samples of patients with COPD and the relation with the occurrence of AE.

Material and methods: From March 2009 until August 2010 sputum samples of COPD patients clinically rehabilitating at the centre of expertise for chronic organ failure (CIRO), were included. Patients were followed during an 8 week period and sputum samples were collected during the stable state and during an AE. Real-time PCR for respiratory viruses, including rhinovirus and hMPV, was performed.

Results: A total of 498 sputum samples (218 patients) were included, 257 samples (52%) were collected during the stable phase. Viruses were detected in 64 (25%) of the stable samples. The most frequently isolated viruses in the stable samples were hMPV (12%) and rhinovirus (12%). A total of 74 patients experienced an AE in the weeks after stable sample collection, of which 12 (16%) had hMPV in the stable sample. Patients with hMPV in the stable phase experienced significantly more AEs in the first weeks after sample collection compared to patients without hMPV (or any other virus) (p=0.03).

Conclusion: hMPV was one of the most isolated viruses in samples collected during the stable state. Patients with hMPV in the stable sample experienced more exacerbations compared to patients without any virus in the stable sample.

P3009
Ammoxcin concentrations in sputum in relation to beta-lactamase activity in COPD patients
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Introduction: COPD exacerbations are often treated with antibiotics, although their use is controversial. A previous study showed that patients with a sputum concentration of amoxicillin (a beta-lactam antibiotic) lower than the minimum inhibitory concentration (MIC<2 mg/l) were hospitalized 4 days longer then patients with a concentration ≥MIC90. One explanation for a low amoxicillin concentration could be that patients’ lungs are colonized or infected with pathogens that have beta-lactamase activity.

Objective: This study investigated if beta-lactamase activity was higher in patients who had a sputum amoxicillin concentration <2 mg/l than in patients with a concentration ≥2 mg/l.

Methods: 23 Hospitalized COPD patients treated with amoxicillin/clavulanic acid for an acute exacerbation were included. Sputum and serum samples were collected at the third day of treatment to determine beta-lactamase activity in sputum and amoxicillin concentrations in both sputum and serum.

Results: We found no difference in beta-lactamase activity between patients with a sputum amoxicillin concentration <MIC90 and ≥MIC90 (p=0.79). Amoxicillin concentrations were <MIC90 in 18 out of 23 sputum samples (78%). Serum concentrations amoxicillin were <MIC90 in 7 patients (30%).

Conclusions: Beta-lactamase activity did not differ between patients with sputum amoxicillin concentrations <MIC90 or ≥MIC90. The finding that a majority of patients had a sputum amoxicillin concentration <MIC90 suggests that these patients are being undertreated. Further research could focus on inhalation of amoxicillin to obtain higher concentrations in sputum.

P3010
Clinical and economical impact of exacerbations of chronic obstructive pulmonary disease (COPD): A two-year study
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COPD is a common disease with considerable health and economical consequences. The aim of our study was to analyze clinical and economical impact of COPD exacerbations (E-COPD). A secondary data analysis of healthcare administrative databases of Lombardy, Italy, was performed, including patients hospitalized for a severe E-COPD (index event) from Jan to Dec 2003. Two study groups were identified based on the number and type of E-COPD experienced during the follow-up: those who had at least one severe E-COPD (Group A) and those who had only moderate E-COPD (Group B). A total of 12,436 patients (7,933 males; mean±SD age: 74±10 yrs) were enrolled. Among those, 45% belonged to Group A and 55% to Group B. Clinical outcomes, costs and consumptions of pulmonary function test (PFT) per person during the follow-up are given in Table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths</th>
<th>PFTs cost</th>
<th>Hospitalization cost</th>
<th>Prescription cost</th>
<th>E-COPD, mean (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1,501 (27)</td>
<td>1,502 (22)</td>
<td>9,699 (9,999-9,929)</td>
<td>6,647 (4,526-4,779)</td>
<td>6,3 (3,4-9,85)</td>
</tr>
<tr>
<td>Group B</td>
<td>1,542 (152-1,582)</td>
<td>1,195 (2,813-3,026)</td>
<td>2,916 (2,813-3,026)</td>
<td>1,523 (1,512-1,534)</td>
<td>1,523 (1,512-1,534)</td>
</tr>
</tbody>
</table>

Cost in EURO. *p<0.01 Age-adjusted difference between groups.

Mortality risk increased in the study population in relation to the number and type of E-COPD experienced during the follow-up. The number and type of
E-COPD significantly impact outcomes and costs. Less than one fourth of patients discharged after an E-COPD will undergo a PFT during two years, although this cost is extremely lower than the hospital stay.

P3011 Safety and pharmacokinetics of multiple-dose ciprofloxacin dry powder for inhalation in patients with moderate or severe COPD
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1Clinical Pharmacology, Bayer Schering Pharma AG, Wuppertal; 2Germany; 3Klinische Atemwegsforschung, Frauenhofer Institute for Toxicology and Experimental Science, Hannover, Germany; 4Klinik fuer Pneumologie, Medizinische Hochschule Hannover, Hannover, Germany

Introduction: Many patients with COPD are chronically colonized with bacteria and could benefit from long-term antibacterial therapy. Ciprofloxacin dry powder for inhalation (DPI) is an investigational PulmoSphere™ formulation for pulmonary delivery of ciprofloxacin.

Aim: To investigate the safety, tolerability and PK of ciprofloxacin DPI in patients with COPD.

Methods: In a randomized, phase I, single-blind, parallel-group study, adults with GOLD stage II or III COPD received 32.5 mg or 48.75 mg ciprofloxacin (50 mg, 75 mg ciprofloxacin DPI, respectively) or matching placebo as a single dose on Day 0 and 12 and bid on Days 2-11.

Results: Patients received 32.5 mg (n=6) or 48.75 mg (n=9 including 3 who dropped out) ciprofloxacin, or placebo (n=6). There were no severe or serious AEs; most AEs were mild in severity. There were treatment-related AEs in 4, 8 and 1 patients in the 32.5 mg and 48.75 mg ciprofloxacin and placebo groups, respectively. Three patients discontinued (48.75 mg ciprofloxacin) due to AEs. Treatment-related dyspnoea (n=4), infectious diseases (n=2). Day 0 geometric mean plasma ciprofloxacin AUC(0-24) h=0.532 mg*h/g and 0.727 mg*h/g, and AUC(0-t) h in induced sputum was 1.90 mg*h/ml and 2.010 mg*h/ml, for the 32.5 mg and 48.75 mg groups, respectively. Ciprofloxacin sputum concentrations were highly variable.

Conclusion: Ciprofloxacin DPI was well tolerated over 12 days’ treatment in patients with moderate or severe COPD. High sputum concentrations contrasted with low systemic exposure.

P3012 Does presence of multiple viruses in the stable state predispone COPD patients to exacerbations?
Marijke Vanpaauwen1, Frits Franssen2, Cathrien Bruggeman1, Emiel Wouters3, Catharina Lissen3
1Medical Microbiology, Maastricht University Medical Centre, Caphri School, Maastricht, Netherlands; 2Centre of Expertise for Chronic Organ Failure, Horn, Netherlands; 3Respiratory Medicine, Maastricht University Medical Centre, Maastricht, Netherlands

Introduction: Respiratory viruses are associated with acute exacerbations (AE) in patients with COPD, but may also lead to asymptomatic carrier status. This study investigates whether co-detection of viruses in the stable state predisposes for AEs in patients with COPD. Since it is known that many viruses circulate during the year we wanted to detect the most important respiratory viruses in our study.

Material and methods: From March 2009 until August 2010 sputum samples of COPD patients clinically rehabilitating at the centre of expertise for chronic organ failure (CBO), were included. Sputum samples were collected during the stable state and during an AE. Real-time polymerase chain reaction for rhinovirus, hMPV, RSV, influenza A and B and parainfluenza 1-4, was performed.

Results: A total of 1650 sputum samples (218 patients) were included. Viruses were detected in 208 samples (42%) of which 106 (51%) were collected during the stable state. In 11% of the samples multiple viruses were found, of which the combination of rhinovirus and hMPV was the most frequent (58%). Patients with multiple viruses in the stable sample did not experience more AEs in the first weeks after stable sample collection than patients with a single virus or without a virus in the stable sample.

Conclusion: In 11% of sputum samples of COPD patients multiple respiratory viruses were found. The presence of multiple viruses does not predispose these patients to the short-term occurrence of an AE.

P3013 The relationship between PBMC secretion of IFN-alpha following TLR7 and TLR9 activation and lung function in COPD
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Introduction: Viral and bacterial infections play a key role in exacerbations in COPD. IFN-alpha has been implicated in the persistence of symptoms. The relationship of the inflammatory response to these airway pathogens at stable state and exacerbations is also poorly understood and how this may lead on to structural airway remodelling is poorly defined. We sought to investigate the relationship between clinical parameters in COPD and the in vitro response to TLR 7 & 9 activation.

Method: PBMCs were stimulated for 24h, with 10μM R848 and 1μM CpG, from healthy controls & COPD subjects. IFN-α release was measured in supernatant using ELISA kits.

Results: COPD & healthy control subjects were recruited. The mean (SD) FEV1 (% predicted) (L) & FEV1/FVC of the COPD subjects was 1.32 (0.58) & 0.5 (0.13) respectively. There was no significant difference in IFN-α (pg/ml) release when comparing health 74 (30) to COPD 59 (42) (p=0.33) when stimulating TLR 7. TLR 9 stimulation gave a significant increase in IFN-α production in COPD 204 (106) vs health 114 (61) (p<0.003). TLR 9 stimulation was significantly increased compared to TLR7 in COPD (p<0.001). There was a significant negative correlation with lung function and TLR 7 stimulation in the COPD group, FEV1 (r=-0.46, p=0.005); FEV1/FVC (r=0.37, p=0.024); FEV1/FVC (r=0.39, p=0.002). TLR 9 stimulation had a significant negative correlation with lung function, KCO% predicted (r=-0.55, p<0.001) and TLC% predicted (r=-0.43, p=0.01).

Conclusion: The release of IFN-α by PBMCs was increased in COPD compared to healthy controls following TLR 9, but not TLR 7 stimulation. The IFN-α release after TLR7 & 9 activation was related to lung function.

P3014 Bacterial load in chronic obstructive pulmonary disease and its relationship with airway inflammation and lung function
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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is characterised by fixed airflow obstruction, typically in association with persistent airway inflammation and bacterial colonisation. The relationship between these features of disease is not fully understood.

Method: Patients with COPD were recruited from a single centre and were characterised in terms of their lung function, health status, sputum cell counts and quantitative microbiology to derive colony forming units (CFU)/ml of sputum.

Results: 126 patients were recruited, 83 were male. The mean (SEM) was for FEV1% predicted: 48.10 (1.64), sputum neutrophil count 73.2 (2.06%), total cell count (TC) 6.65 (0.98) ×106/μl, CFU 8.5×105-1.5×106/μl and median (IQR) eosinophil count 0.75 (0.25-2.50)%. Univariate correlations was observed between CFU and neutrophil (%) (r=0.306, p<0.001), TCC (r=0.273, p=0.002), but not eosinophil (%) (r=0.058, p=0.517) and FEV1% predicted (r=0.061, p=0.497).

Conclusion: Bacterial load was associated with the sputum total cell count and neutrophil differential but was not associated with lung function. Longitudinal studies are required to assess the role of bacteria in disease progression.

P3015 Induction of cathelicidin (LL-37) in rhinovirus-induced COPD exacerbations
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Cathelicidin (LL-37) is a cationic antimicrobial peptide and has both antimicrobial and immunomodulatory effects. The majority of LL-37 is stored in neutrophil granules for release at sites of infection. LL-37 has demonstrated anti-viral effects but the role of LL-37 in virus-induced COPD exacerbations is unknown.

Method: We infected 3 groups of subjects—COPD GOLD stage B (N=20), smokers with normal lung function (SMK, N=21) and non-smokers (NS, N=11)—with rhinovirus 16 (RV). Induced sputum was post-collected. In a subset of COPD (N=10) and SMK (N=12) BAL was collected on day 7. Sputum and BAL cytospins were prepared and cell counts determined. LL-37 and cytokines were measured in sputum supernatants by ELISA and virus load by quantitative PCR.

Results: In all subjects combined post-infection peak sputum LL-37 levels correlated with peak sputum virus load (P=0.0018, r=0.43) and peak sputum total inflammatory cells (P<0.0001, r=0.72). These correlations were also significant in the COPD group alone (P=0.017, r=0.53 and P<0.001, r=0.85 respectively) but not in the NS or SMK. In BAL LL-37 correlated with BAL virus load (P=0.044, r=0.64), pro-inflammatory cells (P<0.0001, r=0.89), neutrophils (P<0.001, r=0.98), IL-8 (P<0.0001, r=0.83), TNF-α (P<0.001, r=0.87) and IL-6 (P=0.002, r=0.63). These correlations were also significant in the COPD group alone but not in the SMK. LL-37 in sputum and BAL following rhinovirus infection correlates with inflammatory cells, pro-inflammatory cytokines and virus load. Further studies are required to determine whether LL-37 contributes to neutrophilic inflammation in virus-induced exacerbations or is a component of the anti-viral innate immune mechanism.
Introduction: Self-similarity in Peak Expiratory Flow (PEF) can predict the frequency of asthmatic events but it is unknown whether in COPD there is a relationship with exacerbation frequency.

Methods: We examined data from the London COPD cohort on 308 COPD patients who recorded worsening of respiratory symptoms and PEF on daily diary cards. Exacerbations were identified as previously described (Seemungal. AJR-CCM 157: 1418-1422, 1998) from which an annual rate was calculated. Detrended fluctuation analysis was used to calculate α which is a measure of decay in self-correlation over time (Frey et al. Nature 438: 667-70, 2005). PEF time series when the patient was clinically stable were also analyzed by excluding data collected 1 day before to 7 days after each exacerbation, and splitting the series together.

Results: The 308 COPD patients (195M; mean age (SD) 68.3 (8.4) years; FEV1 1.12 (0.42) l, FEV1/FVC 0.53 (0.27) l, PEF% predicted 54.7 (18.6). The cohort recorded diary card data for a median 1077 days and experienced 2621 exacerbations with a median frequency of 2.04 per year (IQR 0.9 – 3.3). The patients had an α of 0.944 (SD 0.19) over the initial 365 days which was positively related to exacerbation frequency (negative binomial regression, P=0.009). No difference was seen if exacerbation PEF data were excluded, α = 0.935 (SD 0.21; P=0.139) and there was also a relationship with exacerbation frequency (P<0.001).

Conclusion: In COPD patients, long-term correlations (self-similarity) exist in PEF which are related to exacerbation frequency. The exponent α may prove a useful marker of exacerbation frequency and as normally distributed lead to a reduction in the number of patients required for clinical trials.

P3017
The role of respiratory virus infection in COPD exacerbations
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1Pneumology, Corporació Sanitària Parc Taulí, Sabadell, Barcelona, Spain; 2Microbiology, Corporació Sanitària Parc Taulí, Sabadell, Barcelona, Spain; 3Microbiology, Hospital Clinic, Barcelona, Spain

Aim: To determine the prevalence of viral infection in a cohort of severe COPD patients.

Methods: We conducted a prospective observational study in a cohort of severe COPD patients from 2005 to 2007. We recorded for each exacerbation: etiological agent, prior antibiotic prescription, corticosteroid treatment and days of hospitalization. Sputum samples were collected and the Gram staining Murray-Washington’s grade was done. A multiplex retrotranscriptase-nested PCR assay was used for simultaneous detection of Parainfluenza virus (1, 2, 3, 4AB), human Coronavirus (229E and OC43), Enterovirus, Rhinovirus, Influenza virus A, B, C, Respiratory syncytial virus and Adenoviruses following the procedure described by Costat et al. (J Med Virol 72:484-95).

Results: A total of 118 patients were registered with a mean age of 69.4±8 years. The 60% were in GOLD stage IV. Among the 307 respiratory samples processed 89 (57.5%) were Murray grade IV and 66.1% (203) of them had positive respiratory bacterial pathogen (positive cultures). Overall, virus were detected in 110/307 (35.8%) of analyzed samples, being Rhinovirus the most common of them (22%). In 51.5% (377/2) of bacterial negative cultures samples virus were detected, while in 31% (63/203) of bacterial positive cultures virus co-infection was observed (p<0.05).

Conclusions:
– The prevalence of viral infection in our cohort was 36%, being Rhinovirus the most common virus.
– A respiratory viral infection may be suspected in COPD exacerbations among patients with negative bacterial culture.

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P3018
Presence of Pneumocystis jiroveci colonization in patients with COPD
Marijke Vanspauwen1, Frits Franssen2, Cathrien Bruggeman1, Emiel Wouters2,3

1Medical Microbiology, Maastricht University Medical Centre, CAPHRI School, Maastricht, Netherlands; 2Cnr+, Centre of Expertise for Chronic Organ Failure, Horn, Netherlands; 3Respiratory Medicine, Maastricht University Medical Centre, Maastricht, Netherlands

Introduction: Pneumocystis jiroveci infections are frequently detected in immunocompromised patients. However, evidence suggests that P. jiroveci can be detected in non-immunocompromised patients, where it colonizes the airways. Over the past years, P. jiroveci has been linked with COPD. P. jiroveci colonization may be associated with the severity of COPD and some evidence suggests a role for P. jiroveci in the progression of COPD in smokers. The present study investigates the presence of P. jiroveci in sputum samples of patients with COPD.

Material and methods: From March 2009 until September 2010, sputum samples from COPD patients at the centre of expertise for chronic organ failure (COPD) were included. Patients were followed during an 8 week period and sputum samples were collected during the stable state and during an acute exacerbation (AE). Sputum samples were analyzed for the presence of P. jiroveci by a real-time PCR assay.

Results: During the study period 509 sputum samples (218 patients) were collected clinically rehabilitating at CIRO Horn. A total of 184 samples (36%) were collected during the stable phase and 325 (63.8%) during an AE. P. jiroveci DNA was detected in 40 (8%) of all sputum samples. A total of 23 positive samples (57.5%) were detected during an AE and 17 during the stable state (42.5%).

Conclusion: In our population, P. jiroveci colonization could be detected in 8% of the sputum samples of COPD patients. Additional research is needed to clarify the role of P. jiroveci in the pathophysiology of COPD.
P3021 Characteristic of cytokines levels of blood and sputum in COPD exacerbation

Sofya Nesterovich1, Ekaterina Bukreeva2.

In this double blind placebo controlled study, we analyzed the immunological effect of PMLB, administered to a population of elderly Chronic Obstructive Pulmonary Disease (COPD) patients.

Methods: The treatment provided 1 tablet of PMLB for the first ten days of the month, followed by a 20 day rest. The treatment was repeated for other two months and the follow up was carried out up to six months. Blood cell samples were collected at time 0 (before the beginning of the study), after three months and after six months.

Results: CD4+ and activated T cells increased significantly in treated group, while Treg were significantly reduced. Transitional B cells (in particular T3) were recruited and associated to an increase of early naive B cells; recruitment of early memory cells was associated to a reduction of “classic” memory B cells. Finally, NK cells were significantly increased in treated patients, while their subpopulations remained unaltered.

Conclusion: In conclusion, PMLB administration causes in COPD patients an important recruitment of cells belonging to the innate immune system, such as NK, a significant activation of early B cell compartments and a clear reduction of regulatory T cells associated to the increase of T cell activation. All these findings confirm that, also in COPD patients, a specific (and also partially polyclonal) activation of B cells occurs, and this seems to be strictly related to the significant clinical results observed.

P3024 Role of endothelial dysfunction, disturbance of haemostatic reactions in pathogenesis of acute exacerbation of chronic obstructive pulmonary disease (AE COPD)


Purpose: It is to research interrelations of endothelial dysfunction, system inflammatory and haemostatic reactions at patients with AE COPD.

Materials and methods: In open prospective clinical investigation 111 patients with 2 or 3 positive criteria Anthonisen et al. (1987) were included. Men were 91 people (82%), women - 20 people (18%). The smoking index was 37.5±2.06 pack-years. Patients with AE COPD divided on two subgroups: 1st - patients without bronchoctasia, 2nd - patients with bronchoctasia. All patients received therapy system glucocorticoids. The control group included 53 healthy non-smoking people with middle age 25.9±1.36 years, from them 27 (51%) men and 16 (29.9%) women. It was accomplished immunoenzyme definition of CRP, endotelin-1, D-dimers and homocystein maintenance in blood before treatment.

Results: Direct correlation communication between indexes CRP and endotelin-1 (r=0.80, p<0.001), indexes CRP and D-dimers (r=0.65, p<0.01) in the AE COPD was observed. Dynamics of indexes of endothelial dysfunction and thromboembolic risk at patients with various phenotypes AE COPD are in table 1.

Table 1

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Control group</th>
<th>Patients subgroup 1</th>
<th>Patients subgroup 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>3.3±0.14</td>
<td>6.5±1.97</td>
<td>13.3±3.24*</td>
</tr>
<tr>
<td>ET-1 (fimod/ml)</td>
<td>0.3±0.04</td>
<td>1.8±0.55*</td>
<td>1.2±0.38*</td>
</tr>
<tr>
<td>D-dimers</td>
<td>0.16±0.09</td>
<td>0.60±0.12*</td>
<td>1.64±0.45*</td>
</tr>
<tr>
<td>*Patients subgroup vs. control group p&lt;0.05</td>
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</table>

Conclusion: At patients with AE COPD it is increased levels of D-dimers, which indicates that specifies on thromboembolic and thromboembolic risks.

P3025 Invasive pulmonary aspergillosis in patients with severe COPD. Comparative study between probable invasive infection and colonization

Rosana Blavia1, Antonia Filliez2, Isabel Serra3, Montse Morta4, Dolores Entvill3, Ramon Trullas5, Damian Perich1, Esperanza Martin1, Conxa Perez4, Emilio Marquilles2.

Background: Efficacy of Polymethyl Cellulosic Bacterial Lysate (PMLB) in increasing the secretion of specific IgA directed to the bacterial antigens administered has been shown.

Aims and objectives: In this double blind placebo controlled study, we analyzed the immunological effect of PMLB, administered to a population of elderly Chronic Obstructive Pulmonary Disease (COPD) patients.

Methods: The treatment provided 1 tablet of PMLB for the first ten days of the month, followed by a 20 day rest. The treatment was repeated for other two months and the follow up was carried out up to six months. Blood cell samples were collected at time 0 (before the beginning of the study), after three months and after six months.

Results: CD4+ and activated T cells increased significantly in treated group, while Treg were significantly reduced. Transitional B cells (in particular T3) were recruited and associated to an increase of early naive B cells; recruitment of early memory cells was associated to a reduction of “classic” memory B cells. Finally, NK cells were significantly increased in treated patients, while their subpopulations remained unaltered.

Conclusion: In conclusion, PMLB administration causes in COPD patients an important recruitment of cells belonging to the innate immune system, such as NK, a significant activation of early B cell compartments and a clear reduction of regulatory T cells associated to the increase of T cell activation. All these findings confirm that, also in COPD patients, a specific (and also partially polyclonal) activation of B cells occurs, and this seems to be strictly related to the significant clinical results observed.
days as opposed to 13±22 d. in colonization (p<0.003) and respiratory failure (80% IPA v 36% p<0.009). Antifungal therapy was received by 91% of IPA and by 36% of colonized. The overall mortality rate was 47% in IPA and 23% in colonization.

Conclusions: 1. Immunosuppression by corticosteroids in COPD patients Gold III-IV is the major risk factor for invasive aspergillosis. 2. The absence of clinical improvement in correctly treated exacerbations of severe COPD and recurrent isolation of aspergillus in sputum should point to the possibility of the existence of IPA and demand a HRCT scan. 3. HRCT findings can detect early IPA in the shape of bronchial spread once bacterial or mycobacterial infections have been ruled out.

### 330. Quality control in lung function and exercise-related issues

#### P3026
**Over-reading spirometry – Man or machine?**
Aleck Harrison1, Grant Sowman2, Hardip KaurNagra2.1 Clinical Research, AJH Partners, Wallingford, Oxon, United Kingdom; 2Pharmaceutical Research, Vitalograph Ltd, Maids Moreton, Buckingham, United Kingdom

The quality of spirometry improves in multicentre trials with the aid of over-reading and prompt feedback to sites [1]. Recently spirometer software has become more sophisticated with increased built-in quality control. So is there a need for human intervention? An international trial with 519 asthmatic patients from 78 sites over 17 weeks produced 7297 spirometry sessions. The site spirometer program (Vitalograph Spirotrak®) determined the acceptability of each session with immediate feedback allowing the investigator to make decisions on the patients involvement. All sessions were e-transferred to the database and full visual inspection of the spirometry curves made by three expert over-readers with feedback within 48hrs, reading to sessions were e-transferred to the database and full visual inspection of the spirometry curves made by three expert over-readers with feedback within 48hrs, reading to validations of the Spirometry 360 program.

<table>
<thead>
<tr>
<th>Session acceptance</th>
<th>Machine Read</th>
<th>Over-Reader</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Accepted</td>
<td>7631</td>
<td>96.7</td>
</tr>
<tr>
<td>Rejected</td>
<td>296</td>
<td>3.7</td>
</tr>
</tbody>
</table>

The shape of both curves for rejected sessions follows that seen in other trials, the slope having been demonstrated to be due to prompt feedback. In studies with no feedback the rejection rate is constant [1]. Although there were small differences, this analysis demonstrates that despite hard objective parameters built into software there still needs to be the expert quality of the over-reader's eye.

References:

The trial sponsors are thanked for the anonymous use of their data.

#### P3028
**Spirometry 360 on-line training and feedback: Spring 2011 course results and future plans**
James Stout, Karen Smith, Bruce Culver, Allen Dozor. Department of Pediatrics, University of Washington, Seattle, WA, United States Department of Pediatrics, University of Washington, Seattle, WA, United States Pulmonary and Critical Care, University of Washington, Seattle, WA, United States Pediatric Pulmonology, New York Medical College, Valhalla, NY, United States

Although office-based spirometry is increasingly gaining acceptance in general practice, wide variations in test quality impede its use. Spirometry 360 is a four-month interactive on-line training and feedback program currently delivered from the University of Washington to primary care practices around the U.S. It consists of: 1) Spirometry Fundamentals, a multi-media tutorial and reference tool; 2) interactive, case-based webinars led by clinical experts, and 3) an internet-based quality feedback reporting system that summarizes technique of de-identified spirograms automatically uploaded from the point of care.

We delivered the training for the second time in 2010 to 23 general practices from 4 states around the U.S. Results included a doubling of the acceptable spirograms for children younger than eight years from 40% at baseline to 80% at the end of training, and an overall increase in the acceptable spirogram rate from 49% to 71%. Among course participants, 100% reported that they would recommend the training to a colleague.

We are now delivering the course from February to June in 2011 in two concurrent tracks to 70 pediatric and family practices, involving over 200 physicians and their support staffs from 35 states around the U.S.

We will present a detailed analysis of over 4,000 tests from the Spring 2011 course, with a description of the reasons for variance from the ERS/ATS 2005 Spirometry Guideline, to further understand practitioners’ needs when performing office-based spirometry. We will also report on our plans for a "Train-the-Trainer" program with a goal of establishing independent training sites for ongoing delivery of the Spirometry 360 program.

#### P3029
**Stature measurement: Potential for improved interpretation of pulmonary function**
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Introduction: Measurement of stature is a prerequisite for determination of the normal lung function since reference equations are based on stature (standing height).

Objective: The aim of this study was to investigate the optimal method to measure stature in a busy pulmonary function laboratory.

Methods: We measured the stature of 87 subjects using a digital-counter sta-

Agreement between methods in measurement of stature

<table>
<thead>
<tr>
<th>Method</th>
<th>Number</th>
<th>Mean difference, cm</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference Harpenden – Harpenden</td>
<td>10</td>
<td>-0.29</td>
<td>-0.60 to 0.02</td>
</tr>
<tr>
<td>Difference Harpenden – bench rule</td>
<td>87</td>
<td>-0.59</td>
<td>-0.70 to 0.49</td>
</tr>
<tr>
<td>Difference Harpenden – ultrasound</td>
<td>86</td>
<td>-0.70</td>
<td>-1.06 to -0.35</td>
</tr>
<tr>
<td>Difference Harpenden – ultrasound ceiling</td>
<td>85</td>
<td>1.36</td>
<td>0.87 to 1.84</td>
</tr>
<tr>
<td>Difference Harpenden – armspan</td>
<td>87</td>
<td>0.45</td>
<td>-0.48 to 1.38</td>
</tr>
<tr>
<td>Difference Harpenden – questionnaire</td>
<td>68</td>
<td>-0.98</td>
<td>-1.48 to -0.49</td>
</tr>
<tr>
<td>Difference Harpenden – interview</td>
<td>46</td>
<td>-1.12</td>
<td>-1.58 to -0.67</td>
</tr>
</tbody>
</table>

Mean difference is an estimate of "trueness" and the 95% Confidence Interval for the difference between individual measurements is an estimate of "precision".
diameter, a wall-mounted bench rule, and an ultrasound distance estimator. Stature was also estimated based on armspan measurement, and self-reported stature was recorded. Results were compared using Bland and Altman plots.

Results: See table. Neither ultrasound measurement nor self-reported stature was sufficiently accurate for clinical use. An unexpected observation was that the stadiometer was the fastest method.

Conclusions: Stature should be measured with the same accuracy as pulmonary function since clinical decisions are based on both. Present the most accurate and probably the fastest measurement of stature is obtained by using a stadiometer with a digital counter.

P3030
Spirometry quality in patients with COPD
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Background and significance: Many spirometries are performed on sick and elderly COPD patients. There is a general perception that it is difficult for such patients to perform spirometries. The 2005 ATS/ERS guidelines on spirometry recommends a repeatability of 150ml for FEV1 and FVC and 100ml if FVC < 1 litre. Our aim was to assess the repeatability criteria in COPD patients.

Methods: Spirometry was performed by 156 patients of COPD. Spirometry was conducted to obtain at least acceptable flow volume loops using spirometers meeting ATS/ERS standards. 131 patients with acceptable spirometry were evaluated for repeatability criteria and 40 COPD patients were evaluated for within individual repeatability criteria.

Results: Of the 156 patients of COPD, 131 (83.9%) had acceptable spiromograms. 92% were males, mean (SD) age = 64 (7.8), mean (SD) FEV1% = 45.7 (14.76). After the usual exclusion criteria and COPD patients. For each test, the difference between the best and second best of 3 trials was calculated for FEV1 and FVC; 10) cough or variable cooperation; 100) FET > 6s. If the error 100 (lack of plateau) would have been omitted. The time needed to obtain acceptable values varied between 4 and 16 minutes (mean 9, mode 7 minutes), without counting interpretation, patient or device preparation, and infection control procedures.

We conclude that 6.4% of aged persons were not able to cooperate during spirometry. Those who cooperated - had problem with reaching the plateau at end expiration. Following errors are recognized: 1) less than 3 trials; 2) lack of reproducibility of FEV1 and 4) FVC; 10) cough or variable cooperation; 100) FET > 6s or lack of plateau; 1000) BEV too high and 4000) abrupt end.

P3031
Quality of spirometry in the elderly
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Assessment of lung function in aged subjects became quite frequent. We have attempted to evaluate quality of spirometric examination in people aged ≥65 years. We have analyzed data from all the patients admitted to the Center of COPD and Respiratory Failure Regional Hospital of Pulmonology in Bydgoszcz in the period June-December 2010. Spirometry was performed by 3 experienced techni- cians using Jaeger’s MasterLab calibrated prior to the measurements. There were 500 patients analyzed (age range: 65-90; median: 72; mean ±SD: 73.1±7.5). We used quality error codes assigned by spirometer (according to ERS/ATS 2005 recommendations for spirometry).

Following errors were recognized: 1) less than 3 trials; 2) lack of reproducibility of FEV1 and 4) FVC; 10) cough or variable cooperation; 100) FET > 6s or lack of plateau; 1000) BEV too high and 4000) abrupt end. Out of 500 patients 32 were not able to perform spirometry (due to error 1 – 28 and 10 – 4). Out of the remaining 468 patients 195 (41.2%) performed spirometry without any errors. In the test – software indicated (by frequency of occurrence) error 100; error 4; error 4000; error 2 and error 1000. In 232 patients 1 error was encountered, in 35 – 2; in 5 – 3 and in 1 – 4. All examined patients reached FET<6s. If the error 100 (lack of plateau) would be omitted, the percentage of good spirometries rise to 91.2%. We conclude that 6.4% of aged persons were not able to cooperate during spirometry. Those who cooperated - had problem with reaching the plateau at end expiration. Such the analysis of errors; repeated from time to time might be very useful in giving feedback to technicians - to make them much more careful in observing end expiration in aged persons performing spirometry.

Reference:

P3032
Number of tests and the time needed to fulfill the quality criteria for plethysmographic measurements
Diana Ionita 1, Carmen Stoicescu 1, Gabriela Weiss 1, Illeana Stoicescu 2, Madalina Burecu 2, Camelia Nita 1, Alina Cioiritur 2, Daniela Dospinu 2, Felicia Cojocaru 2, Ilona Stramblu 1
1 Respiratory Physiopathology Department, “M. Nasta” Institute of Pneumonology, Bucharest, Romania; 2 Clinical Departments, “M. Nasta” Institute of Pneumonology, Bucharest, Romania; Clinical Department, Ascent Clinical Research Solutions, Bucharest, Romania

Objective: To determine the number of tests and the time needed to fulfill the quality criteria for plethysmography.

Subjects and methods: Body-plethysmography was performed in healthy subjects and in patients familiar with the testing, in order to obtain at least three acceptable measurements with repeatable parameters (at least four from the list: Raw, IC, VC, FRC and TLC). The number of tests and the time to obtain quality measurements were noted.

Results: One hundred and eighteen body-plethysmography sessions were performed in 10 weeks: 8 in healthy subjects, 73 in COPD patients and 37 in patients with other respiratory diseases. All the subjects obtained at least 3 acceptable tests and had repeatable values for at least 3 parameters. One hundred and twelve subjects (95%) obtained repeatable values for 4 parameters and 92 subjects (76%) for all the 5 tested parameters. In 13 subjects only 3 tests were needed to obtain repeatable values for the tested parameters, 22 subjects needed 4 tests, 26 subjects – 5 tests, 45 subjects – 6 tests and 12 subjects performed 7 tests. The time needed to obtain correct sessions varied between 4 and 16 minutes (mean 9, mode 7 minutes), without counting interpretation, patient or device preparation, and infection control procedures.

Conclusions: We conclude that the use of biological control subjects to validate exercise testing with supplemental oxygen.

P3033
The use of biological control subjects to validate exercise testing with supplemental oxygen
Kevin De Soomer, K. Leemans, H. Varenberg, W. De Backer, E. Oostven. Dept of Lung Function and Pulmonary Medicine, Antwerp University Hospital, Antwerp, Belgium

Some patients desaturate during exercise due to diffusion limitation of O2-uptake in the lung. To measure their exercise tolerance and its limiting factor, cardiopulmonary exercise testing (CPET) can be performed with supplemental oxygen (O2).

The aim of our study was to validate the High/Low FiO2 software option on the Jaeger Oxycron Pro (Jaeger, Wurzburg, Germany) using biological control subjects. Three healthy lung function technicians (2F: 1M) performed multiple exercise tests, breathing either room air or a gas mixture containing 30% O2 and 70% N2. The exercise test consisted of a 3 min rest period, 3 min unloaded pedaling followed by 5 min steady state exercise at 40 and 80 Watt for the female subjects and 60 and 120 Watt for the male subject, respectively. The mean values of minute ventilation (VE), CO2 production (VCO2), O2 consumption (V'O2) and heart rate (HR) as measured during the last two min of every steady state interval were used for further analysis. Each subject performed 7 tests while breathing FiO2= 21% and 4 tests while breathing FiO2= 30%. Bland-Altman analysis revealed no significant differences were seen in age, gender or FEV1 values between the subjects that obtained repeatable values after 3 or 4 tests versus (vs.) >4 tests, in 3-7 minutes vs. >7 minutes, for 4 vs. 5 parameters (p<NS for all tested associations).

Conclusions: We conclude that using the High/Low FiO2 software option during CPET, V'CO2 and V'O2 are reliably measured while breathing 30% O2.
P3034
Novel strategies for quality control of forced spirometry
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1 Department of Pulmonary Medicine (ICT), Hospital Clinic - IDIBAPS: Centro de Investigación en Red de Enfermedades Respiratorias (CibeRes), Barcelona, Spain; 2Department of Pulmonary Medicine, Hospital de Cruces - Centro de Investigación en Red de Enfermedades Respiratorias (CibeRes), Bilbao, Spain; 3Oficina d’Estàndards i Interoperabilitat TicSalut, Departament de Salut, Generalitat de Catalunya, Barcelona, Spain; 4Department of Pulmonary Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 5Tecnocampus, Tecnocampus Materiel-Marcorea, Mataró, Spain.
1Master Plan for Respiratory Diseases, Health Ministry of Catalunya, Generalitat de Catalunya, Barcelona, Spain
High Quality Forced Spirometry (HQS) in primary care (PC) enhances management of respiratory patients. We aimed at: a) developing standards to transfer FS data using DICOM; b) deploying web-based support to PC and Community Pharmacists (CPH); c) validating a new algorithm for automatic assessment of quality of the tests; and, d) assessing the web application
We explored 1430 subjects from 15 PC and 812 subjects from 40 CPH. The follow-up period was >6 months. The validation of the algorithm for automatic QC was done using 778 curves from 291 patients and the 24 flow-volume and volume-time curves from the ATS. The assessment by an expert professional and the score automatically generated through the algorithm were compared (Grade 0, rejected; Grade 1 accepted; and, Grade 2 doubtful test). The percent of HQS increased from 57% to 78% during the study period (9 months). The CPH study showed on average 70% HQS. The performance of the algorithm for automatic assessment of spirometry quality control was acceptable (Sensitivity 96%; Specificity 95%).
Our results prompt the adoption of strategies to standardize the transfer HQS tests (HL7,CDA IC) among providers. Thus, facilitating information sharing across the systems and enhancing the quality of the tests. The automatic algorithm showed high applicability. All together, the study facilitates future strategies for early diagnosis of chronic obstructive diseases as well as long-term follow-up of patients.
Supported by Inforegión, NEXIS (CIP-PSp No 225025), FarmaEPOC and PDMAR.

P3035
Preoperative determinants of the length of hospital stay in patients undergoing surgery for pancreatic cancer
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Introduction: Surgery for pancreatic cancer is associated with considerable morbidity. Both surgeon-related and patient-related factors are important in determining postoperative outcome. Therefore most pancreatic surgery is now carried out in specialist centres. However, patient optimisation is complex since factors that determine postoperative morbidity are less well understood.
Objective: To compare preoperative measures of patient comorbidity with length of hospital stay in patients undergoing pancreatic surgery.
Patients and methods: 103 patients who underwent surgery for pancreatic cancer (pancreatico-duodenectomy n=87, trial dissection with bypass n=16) had preoperative evaluation of body habitus, chronic respiratory disease, diabetes, obesity and cardiac disease (Glasgow Prognostic Score, mGPS) and routine blood analysis. Cardiopulmonary function (CPET) was measured in 54 patients. Length of hospital stay was recorded.
Results: The median length of hospital stay was 17 days. 39 stayed <14 days and 64 ≥14 days. Length of hospital stay was not associated with body habitus or systemic inflammatory response. However, in patients with CPET, more patients with low anaerobic threshold (p=0.030), high base excess (0.056) and high VE/VCO2 (p=0.022) had a hospital stay >14 days. Prolonged hospital stay was associated with pancreatico-duodenectomy (p=0.027) and anastomotic failure (p<0.001).
Conclusions: CPET was the only pre-operative objective measure that correlated significantly with prolonged hospital stay. Length of stay is a useful surrogate marker of post-operative adverse events. Although CPET does not predict specific complications, it may determine the host response to major surgery and its immediate sequelae.

P3036
Is there a difference between the results of the standard six minutes walking test (6MWT) and the test with ventilation monitoring (V6MWT)?
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Background: 6MWT is a validated test for the evaluation and monitoring of patients with cardiovascular and respiratory conditions. The standard test evaluates the initial and final heart rate (HR) and oxygen saturation (SaO2), and does not measure ventilation.
Aim: To assess (a) the similarities of the main parameters between S6MWT and V6MWT and (b) the mask-related discomfort during V6MWT.
Subjects and methods: 23 patients (P) with respiratory disease (15 COPD cases) and 3 healthy subjects (HS) performed two S6MWT and one V6MWT, at 1 hour intervals. 6MWT distance (6MWd), initial and final HR, SaO2 and symptoms, and the mask-related discomfort were recorded.
Results: The mean 6MWd was 9 meters longer in S6MWT than in V6MWT (range -65, +135 m). In 7P (30%) the 6MWd was significantly different (>50 m) between the tests, with 5 P (22%) walking less and 2P walking more than the V6MWT. The centre of Recerca en Enginyeria Biomédica (CREB-UPC), Universitat Politècnica de Catalunya, Barcelona, Spain; 3Department of Pulmonary Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 4Tecnocampus, Tecnocampus Materiel-Marcorea, Mataró, Spain.
1Master Plan for Respiratory Diseases, Health Ministry of Catalunya, Generalitat de Catalunya, Barcelona, Spain

P3037
Flow limitation at rest may identify a phenotype of chronic obstructive pulmonary disease (COPD)
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Background: Expiratory flow limitation at rest (FL) promotes dynamic hyperinflation (DH) during exercise in COPD patients.
Aim: To evaluate whether a specific FL phenotype can be identified in COPD patients.
Subjects and methods: 48 COPD patients (28 male, FEV1< 50 % predicted) underwent: pulmonary function tests (PFT), cardiopulmonary exercise test (CPET) with assessment of DH, Saint George’s Respiratory Questionnaire (SGRQ), dyspnea scale (MRC), physical activity by Armband. We measured blood haemoglobin (HB) and inflammatory cells. CRP and Pro-BNP: sputum inflammatory cell count and neutrophil elastase. FL was evaluated according to Hyatt by overlapping the tidal and maximal flow-volume curves and categorized as either absent no overlapping, or present any overlapping.
Results: FL was observed in 38/48 COPD patients. Baseline difference between two groups are reported *(p< 0.05)

<table>
<thead>
<tr>
<th>Flow limitation (3B)</th>
<th>Non-flow limitation (1B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 %</td>
<td>51.1 ±17.2</td>
</tr>
<tr>
<td>IC %</td>
<td>76.4 ±20.2</td>
</tr>
<tr>
<td>TLC %</td>
<td>112.1 ±14.1</td>
</tr>
<tr>
<td>TLC %</td>
<td>88.1 ±22.9</td>
</tr>
<tr>
<td>MRC</td>
<td>1.20 ±0.2</td>
</tr>
<tr>
<td>Daily steps</td>
<td>5932 ±3337</td>
</tr>
<tr>
<td>Blood eosinophils %</td>
<td>2.8 ±1.7</td>
</tr>
<tr>
<td>Blood eosinophils %</td>
<td>17.1 ±5.5</td>
</tr>
<tr>
<td>Sputum neutrophils %</td>
<td>5.7 ±10.8</td>
</tr>
<tr>
<td>Sputum neutrophils %</td>
<td>76.6 ±15.4</td>
</tr>
<tr>
<td>Sputum neutrophil elastase</td>
<td>3.6 ±2.6</td>
</tr>
</tbody>
</table>

Only in FL group, VO2kg was correlated (p< 0.05) with MRC, FEV1%, IC%, DLCO%, HB, DS, SGRQ tot%, HB, Pro-BNP.
Conclusions: Flow imitation at rest, as assessed by a simple, non invasive, inexpensive technique, identifies patients with clinical and functional characteristics suggestive of a specific ‘embryoseme-like’ phenotype.

P3038
Ventilatory exercise response at low altitude
Jerica Sinkeldam, Gwenda Commandeur, Herman Groenhoff. Pulmonology, VU University Medical Center, Amsterdam, Netherlands
Introduction: At medium and high altitude there is an increased ventilatory response to sub maximal exercise tolerance due to a decreased aerobic capacity. However little is known about the ventilatory exercise response at sub maximal exercise at low altitude compared to sea level. Therefore we conducted this study to test if the ventilatory response at sub maximal exercise differs at low altitude compared to sea level.
Methods: Nine healthy women were included to perform a maximal submaximal pulmonary exercise test (3 min, 50 and 100 watt), with gas exchange, heart rate and oxygen saturation measurements on a cycle ergometer at sea level and identical measurements at 1560 meters above sea level (Davos, Switzerland).
Results: See Table 1.
Introduction:
Cardio pulmonary exercise testing (CPET) parameters can be measured with the use of a mouthpiece or a breathing mask. In clinical practice, patients often complain about a dry mouth when a mouthpiece is used which possibly influences CPET results. A more comfortable alternative, although with an increased chance of leak, is the frequently used breathing mask. Therefore we hypothesised that ventilatory CPET results measured by mouthpiece or breathing mask could be different.

Aim: To test this hypothesis we conducted this study to estimate ventilatory CPET differences between mouthpiece and breathing mask measurements.

Methods: Twelve healthy subjects performed two (3 minutes/40 watt) incremental maximal CPET measurements with steady state measurements of ventilation (VE) and oxygen consumption (VO2) at sub maximum work levels. The measurements were taken on different days within one week in a different sequence. One using the mouthpiece (dead space: 50 ml) and the other with a mask (Combitox, dead space: 100 ml).

Results: See Table 1.

<table>
<thead>
<tr>
<th>Mouthpiece</th>
<th>mask</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (l/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 watt</td>
<td>20.7±3.6</td>
<td>23.1±2.5</td>
</tr>
<tr>
<td>80 watt</td>
<td>29.3±2.7</td>
<td>32.6±4.3</td>
</tr>
<tr>
<td>120 watt</td>
<td>40.4±3.6</td>
<td>44.6±5.6</td>
</tr>
<tr>
<td>VO2 (ml min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 watt</td>
<td>882±103</td>
<td>884±70</td>
</tr>
<tr>
<td>80 watt</td>
<td>1278±97</td>
<td>1104±84</td>
</tr>
<tr>
<td>120 watt</td>
<td>1094±124</td>
<td>1741±127</td>
</tr>
<tr>
<td>Work (watt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>239±70</td>
<td>232±73</td>
</tr>
</tbody>
</table>

Conclusions: Due to the fact that the VO2 values between mouthpiece and mask measurements were not different, we concluded that the Combitox mask does not leak. However, the VE values measured with the mask were higher compared to those of the mouthpiece. This is likely explained by the higher amount of dead space. The maximum work rate level attained with the mouthpiece or the mask was the same.

P3040
Is measuring ventilation during the six minutes walking test (6MWT) important?
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Background: 6MWD and FEV1 are used as a one-time measure of functional capacity. We aimed to determine the 6MWD for healthy Pakistanis, identify factors affecting 6MWD and derive an equation.

Methods: 15-65yrs subjects were prospectively enrolled after screening. A standardized 6MWT was administered. SpO2, HR, BP and dyspnea scores were determined pre and post-test.

Results: 296 subjects [211 (71%) men] participated with mean age 37.3±12 yrs. The mean 6MWD for all participants was 469.88±101.24m (range 180m – 756m) [men 502.35±92.21m; women 389.28±74.29m]. On univariate analysis gender, weight, height and age showed a significant relationship with the 6MWD. Sub analysis revealed a significant direct relationship between height (r=0.485, p<0.001) and weight (r=0.212, p<0.001). Gender and age were identified as independent factors in multiple regression analysis, and together explained 33% of the variance. The regression equation predicting 6MWD is: 6MWD (m) for men = 164.08 – (1.90 × age) + (1.95 × height) – (0.168 × BMI); for women = 164.08 + (78.06 × age) + (1.194 × height) – (5.68 × BMI) where male gender = 1 and female gender = 0.

Conclusions: In conclusion, the variability of the ISWT is explained largely by gender, age and BMI. The reference values for the ISWT can be adequately predicted using the equation proposed in this study.

P3041
Reference values for the incremental shuttle walking test
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Background: Reference values for the incremental shuttle walking test (ISWT) which are applicable to the whole population are needed.

Objective: The aim of this study was to determine the 6MWD for healthy Pakistanis, identify factors affecting 6MWD and derive an equation.

Methods: 6MWDs among Pakistanis are shorter than predicted by reference equations. The proposed equation gives predicted (mean) 6MWDs for women = 164.08 – (1.90 × age) + (1.95 × height) – (0.168 × BMI) and for men = 164.08 + (78.06 × age) + (1.194 × height) – (5.68 × BMI).

Results:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>6MWD (m)</th>
<th>sea level</th>
<th>1560 meter</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>23.0</td>
<td>174.1</td>
<td>68.4</td>
<td>469.88</td>
<td>463.08</td>
<td>476.64</td>
<td>0.01</td>
</tr>
<tr>
<td>female</td>
<td>23.0</td>
<td>168.1</td>
<td>56.4</td>
<td>439.28</td>
<td>432.08</td>
<td>445.64</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusions: Comparison with published equations revealed a moderate overestimation of the 6MWD in our population.
331. Obstructive sleep apnoea: inflammation and metabolism

P3043
Pulse oximeter validation study
Gelijz Johal, Jodie Hunt, Brendan Cooper. Lung Function & Sleep, Queen Elizabeth Hospital Birmingham, Birmingham, West Midlands, United Kingdom

Introduction: The aim of this study was to assess a) the reliability of our pulse oximeter (SpO2 and HR) signals, b) to detect malfunctions, c) and to provide recommendations on SpO2 testing.

Methods: A pulse oximeter tester (Metron DEAG) was used to test 12 Konica Minolta pulse oximeters over a split 6 month period. The reliability of the analyser was measured against a reference standard (Osram-1 pulse oximeter simulator). The ranges that were simulated include SpO2 of 85%, 95% and 98% at heart rates (HR) of 60, 120 and 140 beats per minute (b.p.m) respectively.

Results: The Bland-Altman analysis did not reveal any significant difference at all 3 ranges for both analysers. The mean differences at SpO2 of 85% and HR of 40 b.p.m was -0.37% and ±2SD of (0.67 – 1.39). At 95% b.p.m mean difference of ±0.67±2SD (+1.8 - +0.15) and 95% at 120 b.p.m a mean difference of 0.08± ±2SD (+0.44 – 0.29). The difference between the two analysers was correlated better towards the higher range of SpO2. There was no variability in the simulated HR during the testing of all the pulse oximeters.

Discussion: The results of the study show that the oximeters appear to be remarkably stable over time.

Conclusions: The change in SpO2 over Period 1 (mean simulated readings of 86.1%, 95.8% and 98.0%) and Period 2 (mean simulated readings of 86.2% and 95.7% and 98.0%) was negligible. The P values for all three ranges (85% P value of 0.65, 95% P=0.59 and 98% P=0.47) were > 0.05 and therefore no significant difference in the data existed. We conclude that regular testing of pulse oximeters does not help predict failure or problems that aren’t picked up by the regular operators.

P3046
Albuminuria in children with obstructive sleep apnea
Vasiliki Varlam1, Emmanuel Axenteopoulos1, Georgia Malakasioti1, Vasiliki Theolog1, Eleni Theophanou1, Athanasios Kaditis1, Efthimia Daskalopoulou2, Konstantinos Gourgoulianis1. Sleep Disorders Laboratory, University of Thessaly School of Medicine and Larissa University Hospital, Larissa, Greece; 2Department of Internal Medicine, Sleep Laboratory, “St Paul” General Hospital, Thessaloniki, Greece

Increased excretion of albumin in urine has been considered a surrogate marker of endothelial dysfunction in adults with obstructive sleep apnea (OSA). Aim of this study was to evaluate urinary excretion of albumin in children with OSA.

Methods: Albumin-to-creatinine ratio (ACR) was calculated in a morning urine specimen collected from children with or without OSA. An assay appropriate for detection of microalbuminuria was used.

Results: Twenty seven subjects with moderate-to-severe OSA (5.6±2.1 y.o.; AHI 9.1±3.7 episodes/h), 71 subjects with mild OSA (6.2±2.3 y.o.; 2.4±1.4 episodes/h) and 31 children without habitual snoring (6.7±2.4 y.o.; 0±0.6±3 episodes/h) were studied. Subjects with moderate-to-severe OSA had similar ACR to those with mild OSA (p=0.072) and significantly higher ACR relative to subjects without habitual snoring (p=0.007): median 0.38 (0.14-1.3) mg/g vs. 0.31 (0.13 vs 0.3, respectively). There was significantly increased risk for having ACR values ≥15 when comparing children with moderate-to-severe or mild OSA compared to children without habitual snoring after adjustment for age and gender: OR (95% CI) 6.4 (1.8-23.3) of 8.4 kg/m2, respectively. OSA was moderate to severe

P3047
Biochemical basis of inflammation in children with obstructive sleep apnea syndrome (OSAS) and in children with obesity
Melania Evangelisti, Anna Claudia Massolo, Filomena Ianniello, Maria Chiara Paolino, Marilisa Barnas, Vasiliki Varlam, Maria Rosaria Bonsignore, Maria Carmela Giordano1, Vincenzo Bellia1, Maria Rosaria Bonsignore 1,2.

Pneumonology and Alergology, Warsaw Medical University, Warsaw, Poland

Introduction: There is evidence that certain endocrine disorders are associated with impaired breathing during the sleep. One of the hormones closely associated with sleep is melatonin. It is a hormone secreted cyclically, which is associated with impaired breathing during the sleep. One of the hormones closely associated with sleep is melatonin. It is a hormone secreted cyclically, which

Aim: The aim of the study was to investigate circadian profile of melatonin secretion in patients with OSAS.

Methods: Study group consisted of 71 patients with OSAS: 66 men (93%) and 5 women (7%). The average age was 49±2,9±1 years. Body mass index was 32.7±4,5 kg/m², mean AHI 45±22.8/hour. OSAS was diagnosed with full polysomnography. In the study group 6 patients (8.5%) diagnosed with mild OSAS, 10 patients (26.7%) moderate OSAS and 46 patients (64.8%) severe OSAS. Control group consisted of 18 subjects with excluded OSAS, mean age 43±13 years, mean BMI 28.7±4.4 kg/m², mean AHI 2.5±2.1. In the study group and control group circadian profile of melatonin secretion was assessed with radioimmunoassay method (RIA) at 6 time points.

Results: Melatonin concentration (pg/ml) at 2.00, 6.00, 10.00 am and, 2.00, 6.00, 10.00 pm were: in the study group 91.8±70.7, 63.2±54.8, 21.4±11.3, 17.8±6.3, 21.1±6.2, 30.1±5.2; in the control group 136.2±93.9, 94.2±2.7, 30.4±2.9, 23.5, 9.3±6.1, 16.5±11.9, 43.6±2.7. Po.05

Discussion: The Bland-Altman method was used to assess the agreement in the two analysers. The mean difference in the data existed was 0.08± ±2SD (+0.44 – 0.29). The difference between the two analyzers was correlated better towards the higher range of SpO2. There was no variability in the simulated HR during the testing of all the pulse oximeters.

Discussion: The results of the study show that the oximeters appear to be remarkably stable over time.

Conclusions: The change in SpO2 over Period 1 (mean simulated readings of 86.1%, 95.8% and 98.0%) and Period 2 (mean simulated readings of 86.2% and 95.7% and 98.0%) was negligible. The P values for all three ranges (85% P value of 0.65, 95% P=0.59 and 98% P=0.47) were > 0.05 and therefore no significant difference in the data existed. We conclude that regular testing of pulse oximeters does not help predict failure or problems that aren’t picked up by the regular operators.

Results: Twenty seven subjects with moderate-to-severe OSA (5.6±2.1 y.o.; AHI 9.1±3.7 episodes/h), 71 subjects with mild OSA (6.2±2.3 y.o.; 2.4±1.4 episodes/h) and 31 children without habitual snoring (6.7±2.4 y.o.; 0±0.6±3 episodes/h) were studied. Subjects with moderate-to-severe OSA had similar ACR to those with mild OSA (p=0.072) and significantly higher ACR relative to subjects without habitual snoring (p=0.007): median 0.38 (0.14-1.3) mg/g vs. 0.31 (0.13 vs 0.3, respectively). There was significantly increased risk for having ACR values ≥15 when comparing children with moderate-to-severe or mild OSA compared to children without habitual snoring after adjustment for age and gender: OR (95% CI) 6.4 (1.8-23.3) of 8.4 kg/m2, respectively. OSA was moderate to severe

Rationale: OSAS and obesity are two risk factors that can lead to the early development of cardiovascular events. These two diseases very often coexist, and it’s hard to understand the mechanisms that characterize each one. Our aim is to determine the different pathways of these two disorders.

Methods: We evaluated 38 children (21±13.5; mean age: 7.68±4.37 years), divided in three groups (18 children with OSAS but non obese, 10 Obese children but without OSA, 10 controls). All children underwent blood sample test for the evaluation of CRP hs, the lipidic and metabolic aspect (Glycemia, Insulin, Cholesterol total, LDL, HDL, triglycerides, leptin, adiponectin, and resistin), the interleuchines pattern (IL-1 a β, IL-2, IL-4, IL-6, IL-2, IL-10, IFN-γ, TNF-α, VEGF, EGF, MCP1) and the polysomnography examination.

Results: OSAS with children and obesity showed showed higher levels of LDL-cholesterol and triglycerides compared to controls (OSAS p=0.005 and p=0.01; Obese p=0.01 and p=0.005). In the obese group leptin levels were significantly higher compared to controls and to the OSAS (p=0.00). In the OSAS groups we found significantly higher levels of IL 1 β (p=0.04) and TNF-α (p=0.05) compared to controls and obese groups.

Conclusions: OSAS and obesity have two different pathways. OSAS promotes an inflammatory pattern through the stimulation of TNF-α, whereas obesity determines an hormonal deregulation especially of the adipokines one, as leptin.
Antiinflammatory medications administered to children with obstructive sleep apnea (OSA) decrease size of pharyngeal lymphoid tissue and severity of airway obstruction. In this study total and cell populations of tonsillar lymphocytes with potential susceptibility to inhibitors of cysteinyl leukotriene receptors.

Methods: Tonsillar tissue excised from children with OSA or controls with recurrent tonsillitis (RT) was studied for expression of types 1 and 2 cysteinyl leukotriene receptors (LT1R and LT2R) by immunofluorescence and flow cytometry.

Results: Ten children with moderate-to-severe OSA (age 5±6.3 years) and 10 subjects with RT (7±4.7 years) were studied. In both children with OSA and RT, immunoreactivity for LT1R and LT2R was detected in CD3+ tonsil T lymphocytes (extracellular areas) and in CD19+ B lymphocytes (germinal centers and mantle zones). In subjects with OSA, LT1R+ fraction of small size CD19+ B lymphocytes (median 26.4%, range 4.7%-77.5%) was similar to the LT1R+ fraction of CD3+ T lymphocytes (5.7%, 0.7%-50.3%) and significantly higher than the LT1R+ fraction of large size CD19+ B lymphocytes (3.3%, 1.3%-31.9%) (p<0.005 and p<0.05). Similar trend was identified for LT2R in children with OSA or RT and for LT1R in participants with RT.

Conclusions: Children with OSA or RT and tonsillar hypertrophy express cysteinyl leukotriene receptors in B lymphocytes of the tonsillar germinal centers and mantle/marginal zones and in extracellular T lymphocytes. These findings explain the beneficial effects of cysteinyl leukotriene receptor inhibitors on pharyngeal lymphoid tissue hypertrophy and OSA.

P3849 Effect of intermittent hypoxia on the expression of fatty acid binding proteins in human adipocytes and macrophages

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Background: Intermittent hypoxia (IH) is a hallmark feature in obstructive sleep apnea (OSA), which is increasingly recognized as an independent risk factor of cardiovascular diseases. Different fatty acid binding proteins (FABPs), including adipocyte (A)-FABP, FABP4 and epidermal (E)-FABP, are now widely accepted as biomarkers associated with increased cardiac-metabolic risks and carotid atherosclerosis. We hypothesize that IH exposure may regulate the expression of two major cell types involved in the development of atherosclerosis, namely adipocytes and macrophages.

Methods: Human preadipocytes and THP-1 cells were cultivated in the differentiation media until reaching final differentiation level of ~80% before treatments. Differentiated cells were exposed to intermittent normoxia (IN) as control or IH (a 10-min hypoxia (5% O2) followed by a 5-min normoxia (21% O2) for 64 cycles using the BioSpherix OxyCycler CS2 system (Redfield, NY)). FABP, Fabp4 and Fabp5 mRNA expressions were measured by RT-PCR, and protein by Western blot.

Results: Adipocytes expressed very high levels of Fabp4 and low levels of Fabp5 while differentiated macrophages expressed high levels of both Fabp4 and Fabp5 consistent with previous reports. IH exposure resulted in an up-regulation of Fabp5 but not Fabp4 expression in adipocytes. Macrophage Fabp4 and Fabp5 levels remained unchanged following IH treatment, suggesting that the two cell types are likely to have distinct functions.

Conclusions: These data suggest that Fabp5 may play a role in atherogenesis in OSA subjects.

P3850 Predictors of obstructive sleep apnea syndrome and metabolic syndrome

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Background: Obstructive sleep apnea syndrome (OSAS) is a well-known factor of cardiovascular disease and is also related with metabolic syndrome (MS). Some factors are predictors of OSAS and also of MS.

Objective: We wanted to know if OSAS and MS have some factors that can predict both diseases. We also wanted to know the prevalence of the individual components of each syndrome as a entity in patients with suspected OSAS.

Patients and methods: We studied all the patients that were referred to our sleep laboratory from January to December 2009. The patients underwent polysomnography and overnight oximetry. OSAS and MS were diagnosed when apnea hypopnea index (AHI) was > 5. MS was diagnosed according to the International Diabetes Federation criteria.

Results: We studied 486 patients; 71.9% were men, with a mean age of 57.3 ± 13.5 years and a body mass index (BMI) 32.1 ± 6.5 kg/m2, 66.9% of patients were diagnosed of moderate-severe OSA. Mean AHI was 30.2 ± 23.8, 93.8% of subjects had enough data to study MS. The prevalence of MS was 64.7%. Hypertension and hyperglycemia increased with the severity of MS (p < 0.001). Age and waist circumference were predictors of OSAS and MS (p<0.05).

Conclusions:
- Central obesity, measured as waist circumference, and age are predictors of both, OSAS and MS.
- MS is more frequent in OSAS patients and its prevalence increases with OSAS severity.
- Hypertension and hyperglycemia are related with OSAS severity.

P3851 Sleep apnea symptoms in diabetes and their first degree relatives

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Background: The purpose of our study was to investigate high risk for sleep apnea syndrome, in a cohort of diabetics and their first degree relatives with different categories of serum glucose level: diabetic, impaired glucose tolerance (IGT), and normal glucose.

Methods: As a part of a cohort study, all of diabetic and their first degree relatives who came for glucose control in diabetes clinic, were invited to take part in the survey. 2,462 individuals (82%) agreed to fill out the Berlin and Epworth sleep questionnaire. Participants consisted of 2462 subjects 15-70 years of age, both males and females. With diabetes and normal glucose, were invited to take part in the survey. 2,462 individuals (82%) agreed to fill out the Berlin and Epworth sleep questionnaire. Participants consisted of 2462 subjects 15-70 years of age, both males and females. With diabetes and normal glucose, were invited to take part in the survey.

Results: Prevalences of high risk for sleep apnea were lowest in first degree relatives with normal glucose group (30.6%) and highest among diabetics (50.5%).

Conclusions: Sleep apnea symptoms are common in first degree relatives of diabetic patients regardless of blood glucose level. Level of blood glucose in Groups with diabetes and abnormal GTT and family of diabetic could not affect sleep apnea symptoms.

P3852 How can identified early presence of atheroclerotic plaque in severe OSAS?

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Carotid plaque is frequent and often unacknowledged in severe OSAS. Ultrasonographic evaluation of the carotid arteries is the safest way to disclose a different level of stenosis in absence of clinical symptoms, but not all OSAS patients are submitted this examination. Nocturnal hypoxemia related to OSAS can induce retinal vessel constriction with a reduction of artero-venous ratio (A VR) evaluated by retinography. Aim of this study was to evaluate in severe OSAS patients a correlation between a severe constriction of AV ratio (< 75) and carotid stenosis, with ultrasonography of the carotid arteries. 30 obese patients (BMI 35±18 kg/m2), aged from 35 to 60 years, non smokers, non diabetics, non cardiopathics, non hypertensive, diagnosed for severe OSAS (AHI=43±22/h) after a polysomnography, underwent retinography of the two eyes with Topcon TCR NW200 non mydriatic retinal camera. 27/30 patients with a severe constricted AVR Index (< 75) underwent ultrasonographic evaluation of the carotid arteries. In 70% (20/27) of this patients ultrasonographic evaluation revealed the presence of plaque at least one of the two carotids. If the pathoanatomic constriction of retinal vessels could be an indirect evidence of carotid artery stenosis, a thrombotic echocardiography and chest computed tomography angiography probably can show also the presence of non calcified coronary plaque in absence of clinical symptoms.
Aim: In this study we focused on the effects of weight loss and SDB on common metabolic parameters.

Methods: Consecutive obese children between 10 and 18 years were recruited. They followed a treatment program with diet, increased physical activity and psychological support. All children underwent a baseline sleep screening and a control study after 4-6 months of treatment in case of diagnosis of SDB. A fasting blood assay was performed baseline and after 4-6 months.

Results: 84 children and adolescents with a median age of 15.1 years (9.5-18.9 years) were included. Mean BMI z-score was 2.73±0.41. 44% of the subjects had SDB. Sleep apnoea severity index correlated positively with HDL-cholesterol (r= 0.34; P=.002), ASAT (r=.33; P=.003) and ALAT (r=.35; P=.001). No correlations were found for glucose, triglycerides and total cholesterol. After weight loss treatment all metabolic parameters improved and only 8% of the patients had residual SDB. Improvements in ASAT and ALAT were mediated by improvements in BMI. Improvements in oxygen desaturation index (ODI) were associated with an increase in HDL-cholesterol (r=.49; P=.003).

Conclusion: This study confirms the link between ASAT, ALAT, HDL-cholesterol and SDB baseline. HDL-cholesterol improved after weight loss in association with improvements in ODI.

P3054
The impact of sleep apnea on glucose metabolism. Results from a long-time follow-up
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Background: It has been suggested that sleep-disordered breathing (SDB) is a risk factor for diabetes, but long-term follow-ups are lacking.

Objectives: To analyze the influence of SDB on future glucose metabolism.

Methods: Men without diabetes (n=141) were investigated with whole-night respiratory monitoring. After a mean period of 11.3 years, they were followed up with an interview, blood sampling and anthropometric measurements. Insulin resistance was quantified using the homeostasis model assessment (HOMA). Delta-HOMA-IR = (HOMA-IRend− HOMA-IRstart)/HOMA-IRstart. An oral glucose tolerance test was performed in 113 men to calculate the insulin sensitivity index. Confounders adjusted for were age, BMI, weight gain, hypertension, treatment for diabetes and years with CPAP during the period.

Main results: At the follow-up, 23 men had diabetes. An apnea-hypopnea index (AHI) >5 and an oxygen desaturation index (ODI) of >5 were significant predictors of developing diabetes. After adjusting for confounders, the association with ODI remained significant (adj. OR 4.4, 95% CI 1.1-18.1). The ODI at baseline was inversely related to the insulin sensitivity index at the follow-up (r = -0.27, p=0.003). A deterioration in HOMA-IR was significantly related to all measurements of sleep-disordered breathing (AHI, AHI>5, ODI, ODI>5 and MeanSatO2) even when adjusting for confounders. When excluding the variable “years on CPAP” from the multivariate model, all associations weakened.

Conclusions: SDB is independently related to the development of insulin resistance and thereby the risk of manifest diabetes mellitus. The results indicate that CPAP treatment can modify this risk.

P3055
Coronary plaque distribution and endothelial dysfunction in younger obstructive sleep apnea patients
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Background: Obstructive sleep apnea (OSA) occurs mainly in middle aged subjects and is associated with a higher incidence of cardiovascular complications.

Aim: Assessment of subclinical cardiovascular risk factors in asymptomatic younger OSA patients.

Methods: Patients undergoing a full polysomnography and with an apnea hypopnea index (AHI)>20, were included. They underwent an echocardiography, a measurement of the carotid intima media thickness (IMT), analysis of the endothelial function (brachial flow mediated dilation, FMD) and a Multislice Computerized Tomography (CT) for determination of the coronary plaque burden. We assessed 13 coronary segments for degree of stenosis (1: normal; 2: 50% stenosis; 3: 70% stenosis; 4: >70% stenosis)

Results: The patients [n=91; age=50±10y; M/F 79/12] had severe OSA, mean AHI of 52.2±23, and 59% had to up eleven coronary segments showing a variable degree of plaque burden. There was a significant correlation between the number of affected coronary segments and IMT (r=0.451; p<0.0001), FMD (r=-0.255; p=0.019), coronary arterial calcium score (r=.546;p<0.001), interventricular septum thickness (r=0.217;p=0.041) and age (r=0.144;p<0.01). Correlations were maintained after adjustment for hypertension, age and smoking. Patients with coronary plaques were elder (54±9y versus 47±9y; p<0.001), had thicker IMT (0.7±0.2mm versus 0.5±0.1mm; p<0.001) and had abnormal FMD (61±1±2% versus 73±3±2.5%; p=.0029).

Discussion: Our results suggest occurrence of significant subclinical coronary abnormalities and endothelial dysfunction in asymptomatic younger severe OSA patients. Routine screening for subclinical cardiovascular risk factors in OSA may be beneficial.

P3057
Endothelial dysfunction in patients with obstructive sleep apnea
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Background: Obstructive sleep apnea (OSA) influences endothelial function and causes cardiovascular diseases.

Objectives: To assess the prevalence of endothelial dysfunction in patients with OSA.

Methods: Twenty-seven obese patients with OSA and 26 healthy obese subjects were investigated. The presence or absence of OSA was evaluated with a sleep study. Endothelial function was investigated with brachial artery ultrasound examination.

Results: Baseline characteristics were equivalent between the two groups. Minimal SaO2 and AH1 in the OSA and control groups were [72.1±6.16 versus 86.5±4.5% (P=0.0000), and 27.9±23.1 versus 2.0±1.5 (P=0.0000)]. There was no statistically significant difference in percentage change 2 of BADSLimitrate between patients and control groups (P=0.05) i.e. endothelial independent dilatation. Flow-mediated dilation (FMD) percentage change 1 was highly significant lower in OSA patients in comparison to control group (Mean ± SD 3.1±2.8 vs 10.6±6.9, (P=0.000) respectively. i.e. endothelial dysfunction. There was positive significant statistical correlation between BMI and BAD (b). FMD and SL Nitrate).Regarding the correlation, there was positive significant statistical correlation between ESS and AH1 the time in which O2 saturation <90%, BADEM and BAdSasal among the patients with OSA, but there was negative significant correlation between ESS and BAD. There was no significant correlation for BMI and OSA. Conclusion: We detected a prominent deterioration in endothelial function in OSA obese patients compared with healthy obese subjects. This deterioration may occur due to ongoing hypoxemia and it may be a possible cause of cardiovascular diseases in patients with OSA.

P3058
A hospital based study of sleep in metabolic syndrome between obese & non obese North Indians
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Metabolic syndrome’s association with sleep apnea is established. However, differences amongst obese and non-obese patients of metabolic syndrome are not clear.

Methods: 50 consecutive patients fulfilling the criteria of metabolic syndrome and their revised National Cholesterol Education Program (NCEP) Adult Treatment Panel-3 guidelines were included. They were divided into two groups based as per revised National Cholesterol Education Program (NCEP) Adult Treatment Panel-3 guidelines were included. They were divided into two groups based on body mass index (BMI) as applicable in Asian Indians-Group I with BMI ≤25kg/m2 and Group II with BMI >25kg/m2. Patients on CPAP therapy & having any other systemic diseases were excluded. All eligible patients underwent overnight polysomnography.

Results: Demographically there was no difference between two groups. The mean BMI of group I & II were 23.2±0.16 6.8 kg/m2 & 31.6±0.93 kg/m2 respectively. Snoring, unrefreshing sleep & daytime sleepiness were the commonest presenting symptoms. Both groups had similar Epworth sleepiness scale. Diabetes & hypertension was significantly higher amongst group I & group II respectively. Both groups had similar sleep time & distribution of all stages of NREM sleep. Group I had an insignificant less REM sleep (7.18±3.23 versus 14.12±2.94, pvalue>0.05). Snoring time was significantly higher among group II (95.8±6.51 vs 44.7±6.29, p<0.001). Apneic episodes were common during NREM sleep in both groups. However the mean apneoa/hypopnea index (AHI) was similar in both groups (34.10±3.04 v/s 32.7±3.09; p value=0.807).

Conclusion: The prevalence of sleep disordered breathing in selective North Indian population with metabolic syndrome irrespective of BMI was high. Community based epidemiological study is the need of hour to define the extent of the problem.

P3059
OSAS and oxidative stress before and after CPAP therapy
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Obstructive Sleep Apnea Syndrome is frequently associated with oxidative stress.
which might contribute to the onset of some of the systemic co-morbidities. Repeated hypoaxia-oxygenation cycles may cause increase in Reactive Oxygen Species (ROS) with a reduction of Nitric Oxide (NO) availability.

This study was undertaken to assess oxidative stress in patients with severe OSAS (Atpnea-Hypopnea index > 30/h) by evaluation of brachial artery Flow mediated dilation (FMD), gp91(phox) and serum levels of nitrite and nitrate (NOx), and to test the hypothesis that Continuous Positive Airway Pressure (CPAP) therapy can reduce oxidative stress.

We choose FMD as indirect marker of endothelial NO-mediated reactivity; gp91(phox) for NADPH oxidase activity and serum levels of NOx, markers of nitric oxide generation.

We enrolled 10 patients with severe OSAS. After polysomnography, for evaluation AHI and oxygen desaturation index (ODI), FMD, gp91(phox) and NOx were measured before and after 90 days of CPAP treatment. None of the patients smoked.

The mean AHI and ODI prior to CPAP were respectively 43.3±11.9h and 35.8±6.2±3.5h, which decreased to 7.6±5.8h and 2.8±1.6h (p<0.001). The mean BMI was 35.3±5.5 kg/m2 and it didn’t change during 90 days of therapy. gp91(phox) decreased from 38.2±7.4 to 23.6±5.1 (p<0.001).

FMD and NOx were not significantly different.

While confirming the association between OSAS and oxidative stress, we found CPAP therapy managed to reduce gp91(phox) in patients who adhered to treatment for at least 4 hours daily, for 90 days, although there was no significant change in body weight.

CPAP treatment could therefore decrease Oxidative Stress in patients with OSAS by correction of apnea and restoring normal oxygenation.

P3060

Cyto megalovirus (CMV) infection – Correlation between CMV-DNA PCR in bronchoalveolar lavage (BAL), CMV pp65 antigen load in PBMCs and clinical symptoms in lung transplant recipients

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Introduction: Cyto megalovirus (CMV) is a significant cause of morbidity and mortality in lung transplant recipients (LITRs) either by causing pneumonitis or by contributing to the development of bronchiolitis obliterans or chronic rejection.

Objectives: Aim of our study was to compare the correlation between CMV-DNA PCR in BAL and CMV pp65 antigen load in peripheral blood mononuclear cells (PBMCs) with the clinical symptoms of LITRs assessed by a clinical score.

Methods: We analyzed 950 BAL samples taken from 73 LITRs during 2007-2009 using PCR and CMV pp65 antigen load in PBMCs. We used a clinical score from 0-10 (defined as symptoms including cough, sputum, dyspnea, exercise capacity, auscultation, temperature) to define a symptomatic or asymptomatic patient. Especially, we compared the clinical score in patients with CMV pp65=0 (n=62) to patients with CMV pp65>0 (n=31).

Results: 73 of the 950 samples (7.7%) were positive either for CMV-DNA PCR in BAL or CMV pp65 antigen load in PBMCs. We found no association between CMV-DNA PCR in BAL and CMV pp65 antigen load in PBMCs. We found a significant correlation between the positivity of PBMCs for CMV pp65 antigen and the clinical score (r=0.31; p=0.006). In patients without CMV pp65 antigen detection the clinical score was 2±0.2 in whereas in patients with CMV pp65 detection the clinical score was 7±4.2.

Conclusion: Assessment of CMV-DNA PCR in BAL does not correlate with the symptoms of CMV infected LITRs. Our results suggest that CMV pp65 is the better predictive marker for symptomatic CMV infection. Further prospective studies to identify patients who need antiviral treatment are necessary.

P3063

Vitamin D deficiency in lung transplant patients: Is it important?

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Introduction: Vitamin D deficiency is getting a lot of attention lately in various pulmonary disorders like COPD and asthma due to its immunomodulatory effect. Moreover a link between disease progression and vitamin D deficiency has been reported. The aim of this study is to evaluate vitamin D deficiency in LTxs patients and to examine effect on lung function.

Methods: Serum 25-hydroxyvitamin D (25(OH)D) levels in blood and lung function (%) (predicted) were measured in 132 lung transplant patients during their yearly check-up post transplant stay (median (IQR) 1067 (371-1448)x2).

Results: Vitamin D deficiency (<30 ng/ml) occurred in 63/132 patients (47.7%).
26 of these patients were severely deficient (<20 ng/ml), while 37 had levels >20 but <30 ng/ml. The FEV1 was significantly lower in the deficient group compared to the group with normal levels. Moreover, there was a correlation between FEV1 and vitamin D levels (p=0.0044 and R=0.25).

Conclusion: Vitamin D deficiency is present in almost half of the lung transplant patients, associated with an impairment of lung function. This clearly shows potential for intervention. This is why we are currently performing a randomized placebo controlled trial about the role of vitamin D supplementation in LTx patients.

MONDAY, SEPTEMBER 26TH 2011

P3064

Association between CT and spirometric changes in azithromycin treatment of chronic lung allograft dysfunction

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Introduction: We investigated the association between CT and spirometric changes in chronic lung allograft dysfunction (CLAD) treated with azithromycin (AZI).

Methods: A cohort of 107 patients with CLAD treated with AZI was retrospectively analyzed for inspiration and end-exhalation thin-section CT findings, as well as spirometry, before and after 3 to 12 m of therapy. CTs were scored by a single observer blinded for the spirometric data. CT and spirometric changes during treatment were correlated using Spearman rank test.

Results: A total of 100 patients had combined CT and spirometric data available at the start and after a median of 6.9 (4.7-11.4) months of treatment. Overall, all evaluated CT changes significantly correlated with the observed spirometric changes, except for MIP 50% (table/figure 1). Correlations between changes in specific CT features (i.e. consolidation and air trapping) and MIP 50% suggest that routine testing for restrictive pulmonary disease may be indicated in CLAD.

Conclusions: AZI treatment of CLAD results in various spirometric changes which are associated with changes in underlying CT abnormalities.

P3066

Montelukast as a rescue therapy for bronchiolitis obliterans syndrome (BOS) after lung transplantation

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Bronchiolitis obliterans syndrome (BOS) is a major cause of mortality and morbidity after lung transplantation (LTX). Montelukast has been shown to be effective in small case series in patients with BOS after LTx and bone marrow transplantation. A retrospective single center analysis was performed in all LTx recipients treated with Montelukast since 1.10.2010 as a rescue therapy for progressive BOS. Montelukast was used in a dose of 10 mg daily as a long-term therapy. All patients with at least 3 weeks of therapy were included. Response and non-response were defined as a confirmed FEV1 of >90% and >110% baseline, respectively. Broncho-alveolar lavage (BAL)-neutrophilia was recorded at baseline.

Conclusions: CT imaging may be of additional value in phenotyping CLAD and may predict response to azithromycin treatment.

P3067

Bronchial carcinoma after lung transplantation, a sobering truth

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The prevalence and mortality due to solid organ tumors after lung transplantation (LTX) steadily increases and we specifically investigated the development of primary bronchial carcinoma (BC) and its outcome after LTX. Out of 470 LTx and heart-LTx Jan 2000 to Dec 2010, 12 patients (2.6%, 8 males) developed a BC at 37.8 (±24.3) months after LTX. They were transplanted at a mean age of 57.5 (±5.1); 8 for emphysema and 4 for IPF; 8/86 single LTx patients (9.3%, 8/86 single LTx patients (9.3%, for emphysema or lung fibrosis) developed a BC in all their native lung, whereas only 4/179 double LTx patients (2.2%, only for emphysema or fibrosis) developed a BC (p=0.021). At diagnosis, 4 patients were in stage I-II, whereas all others in stage III-IV. There were 11 NSCLC (6 adenocarcinoma) and 1 SCLC. Five patients were surgically treated, however, I had unforeseen N2 disease with pleural metastasis at surgery. All other patients (except 2 who died very soon after diagnosis) were treated with chemotherapy ± radiotherapy. The median survival after diagnosis was only 7.5 m, with an almost significant survival difference between patients with stage I-II and stage III-IV disease (p=0.052). The latter patients had a median survival of only 5.5 m versus 21.5 m for the lower stage BC patients (fig).
We conclude that BC especially of the native lung after SLTx is a significant problem and that the survival after diagnosis is very poor, although patients with stage I-II operable disease, tend to do better.

P3068

12 month follow-up of lung recipients with chronic allograft dysfunction treated with extracorporeal photopheresis (ECP)

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A few studies suggest that extracorporeal Photopheresis (ECP) is effective in improving/stabilising graft function in chronic dysfunction of transplanted lung, in analogy to its well documented efficacy in graft versus host disease. At our institution ECP is routinely offered as rescue therapy in all macrocide-resistant CAD patients. Twenty-two pts are currently undergoing monthly ECP treatment, 17 of which have reached a ≥12 month follow-up.

The overall response (defined as a further graft function decline either in FVC or transplantation: A pilot study

Inhaled tobramycin for the prevention of airway stenosis after lung transplantation

P3069

Inhaled tobramycin for the prevention of airway stenosis after lung transplantation: A pilot study

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Purpose: Airway stenosis post lung transplantation (LT) continues to be a significant problem with anastomotic strictures occurring in up to 40% of cases. Despite this data, there is a gap in the literature pertaining to preventative therapies. In this pilot study we examined if inhaled Tobramycin (TOBI) in the postoperative period will decrease the incidence of post transplant airway stenosis.

Methods and Materials: All LT performed between 5/05 and 5/10 at The Johns Hopkins Hospital by a single surgeon were reviewed retrospectively. Using this cohort, patients with and without airway complications were matched for age, gender, diagnosis lead to transplant and use of inhaled TOBI in the immediate post operative period. Patients in the treatment arm received TOBI (2x80mg) for the first 7 days post transplant.

Results: 98 patients underwent LT (86 bilateral, 7 left, 5 right). TOBI was administered to 22 (22.4%). Of the 98 patients, 35 (35.7%) developed airway stenosis at a median of 16 weeks (range 1 to 164 weeks following surgery).

Effect of Postoperative Tobramycin on Airway Stenoses

Of the 22 patients who received inhaled TOBI, 31.8% developed airway complications, 68% of the patients in this cohort who did not receive TOBI developed airway stenosis (p<0.034).

Conclusions: The use of TOBI appears to show a decrease in the development of post operative stenosis in this cohort. Prospective, randomized studies are needed to determine the full efficacy of this therapy.

P3070

Does single lung transplantation actually alleviate the donor pool?

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Objective: Access to lung transplantation is restricted owing to lack of donor organs. Single lung transplantation hypothesitically increases the pool of lung grafts as two recipients can be treated with one donor. In this retrospective study, we evaluated how often both organs were used for single lung transplantsations. If only one lung was transplanted, we analysed cause of no-use of the opposite lung.

Method: On the registry run by the "Agence de biomedecine", we reviewed all single lung transplantations performed in France from 1998 to 2008. Causes of refusal were recorded as follows: second lung not offered by coordinators, lack of blood-group matched single lung recipient, lack of logistic support, size inadequacy regarding the recipient. We compared cause of refusal to the quality of the grafts. Definition of ideal donor included the following: age under 55 years, ventilated less than 48 hours, clear tracheal secretions, PaO2 over 300 mmHg at FiO2 100% and PEP scan H:G, clear chest radiograph.

Results: Lung harvest from 297 donors led to 387 single lung transplantations: both lungs were used for 2 different recipients in 90 donors (180 recipients). In 207 donors, only one lung was transplanted. In 115 donors, the opposite lung was deemed unusable for dissymmetrical quality. In the remaining 92 donors, both lungs were ideal in 34%, and acceptable in 66%. Reasons for no-use were: not offered by the coordinator in 23%, lack of blood-group matched single lung recipient in 19%, size inadequacy in 20%, team logistics in 10% of cases and miscellaneous reasons in 28%.

Conclusion: Communication on organ sharing might increase the number of available donor organs, thus reducing the death rate on waiting list.

P3071

Recipient dependent factors for outcome in a twinned single lung transplantation model

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Objectives: Immediate outcome of lung transplantation will depend on graft quality, surgical conditions and recipient factors. Twinned single lung transplantation is defined as two recipients being treated with lung grafts from the same donor. Recipient dependent factors of outcome can be studied more accurately as graft quality is supposed equal for both recipients.

Methods: We reviewed all single-lung transplantation performed in France between 1998 and 2008. Complete data for the donors were retrieved from the database of the agence de biomedecine. Data concerning the recipient and follow-up after transplantation were retrieved by individually reviewing each medical record. Twinned were identified and compared. Outcome end-points were primary graft dysfunction (PGD) grade 3.

Results: A total of 387 single lung transplantations were performed in 10 French centers: 90 donors led to 180 twinned recipients. Surgical management and medical follow-up did not differ between centers. All used grafts were of good and symmetrical quality. There was no outcome difference between left and right transplantation. Thirty pairs opposed a fibrosis recipient to an emphysemic twin: PGD was significantly higher (p<0.05) in fibrosis. In 28 pairs (31%) outcome was discordant for PGD: fibrosis was significantly more often involved compared to emphysema (p=0.04). Two pairs showed PGD in both recipients while 60 pairs were free of PGD.

Conclusion: Recipient’s prior respiratory disease is a major determinant of outcome. Fibrosis is associated with an increased risk for PGD grade 3. Twinned single lung transplantation could help building risk factor scores for lung transplantation.

P3072

Hyper expanded native lung treated with intra bronchial valves in single lung transplant recipients

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We report four single lung transplant patients, with hyperinflation of the native emphysematous lung, treated with bronchoscopic lung volume reduction using Spiration Intra Bronchial Valves (IBV®). Hyperinflation of the native lung is a common complication to single lung transplantation when treating emphysema. The hyperinflation can lead to compression of the graft and cause respiratory failure. The IBV®’s where used to block airflow in specific parts of the native lung, theoretically reducing the native lung volume thereby relieving the graft.

Methods: We used a protocol consisting of a Krypton SPECT-scan to assess 560s
which lung segments in the native lung had least function. The IBV®'s were placed in the segment or sub-segment. Endpoints were changes in lung function test, 6-minutes-walk-test (6-MWT) and changes in the Krypton SPECT-scan at 3 months follow-up.

Results: Preoperative mean forced expiratory volume in 1 second (FEV1) was 0.62 l (Range 0.45-0.80 l), mean residual volume was 4.57 l (Range 4.01-5.73 l) and total lung capacity (TLC) was 189 m (Range 98-258 m). One patient reported marked improvement of dyspnoea and had a plausible change in lung function but a 6-MWT identical to the preoperative 6-MWT and no changes on Krypton SPECT-scan. The three other patients did not report any clinical changes and did not show any change in lung function. A patient had a marked increase in 6-MWT from 258 m to 360 m, but only a slight improvement on Krypton SPECT-scan. No complications were observed.

Conclusions: This report shows that bronchoscopic lung volume reduction of an emphysematous native lung in single lung transplants using IBV® is feasible and seems safe, although further experience is needed.

P3073

The effect of a murine model of brain death on mechanistic studies on treatment for donor lung injury

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Introduction: Only 15-25% of brain death (BD) donors match the ideal donor criteria for lung transplantation. The mechanisms of BD-related lung injury are not fully understood yet, justifying further research. Materials and methods: Brain death in mice was induced by rapid inflation of a sublumbar balloon catheter. Animals were randomly divided into 4 groups (each 2h sham [S2], 2h BD [BD2], 4h sham [S4], 4h BD [BD4]). Heart rate (HR), mean arterial pressure (MAP) and cortical activity (EEG) were continuously monitored. At the end of the experiment, bronchoalveolar lavage (BAL) was performed and biochemicals were collected for histological analysis.

Results: In both BD groups, the reflex reaction was characterized by a rapid increase in MAP from induction (85.7±6.6mmHg) to hypertensive peak (122.6±16.8mmHg), with normalization of MAP 10 min after BD confirmation (88.6±6.1mmHg). After BD, HR increased significantly (from 322.8±13.2 to 405.0±17.0bpm) and remained high during the rest of the experiment. In the sham groups, HR and MAP remained constant after balloon insertion. A higher number in BAL neutrophils were seen in [BD4] (28.6% ±4.12) compared to [BD2] (3.0% ±3.0), [S2] (1.4% ±1.2) and [S4] (1.8% ±1.4). More neutrophilic infiltration, interstitial oedema and congestion were seen on histology in [BD4] (2.7 ±2.7 and 2.3 ±2.7 respectively) compared to [BD2] (2.1 ±2.3 and 1.6 ±1.9) respectively.

Conclusion: The creation of a BD model in mice to study lung injury was successful facilitating further mechanistic studies to attenuate lung injury at the immunological level using knock-out animals. A 4-hour period after BD is needed for better interpretation of results.

P3074

Determinant factors for bronchial ischemia after lung transplantation

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Objective: Bronchial ischemia is a frequent problem encountered after lung transplantation. The resulting stenosis will delay functional recovery of the graft, reduce nutritional state by body mass index (BMI), duration of cold ischemia, side effects of immunosuppressive drugs and ultimately, the quality of life of the recipients.

Method: With the agreement of 10 French centers, we recorded all single-lung transplantations. The resulting stenosis will delay functional recovery of the graft, reduce nutritional state by body mass index (BMI), duration of cold ischemia and need for renal replacement therapy in ICU (4/8). A higher number in BAL neutrophils were seen [BD4] (28.6% ±4.12) compared to [BD2] (3.0% ±3.0), [S2] (1.4% ±1.2) and [S4] (1.8% ±1.4). More neutrophilic infiltration, interstitial oedema and congestion were seen on histology in [BD4] (2.7 ±2.7 and 2.3 ±2.7 respectively) compared to [BD2] (2.1 ±2.3 and 1.6 ±1.9) respectively.

Conclusion: The creation of a BD model in mice to study lung injury was successful facilitating further mechanistic studies to attenuate lung injury at the immunological level using knock-out animals. A 4-hour period after BD is needed for better interpretation of results.

P3075

Transbronchial lung biopsy after lung transplantation: Different A and B scores with discordant healing process (normal for one recipient opposed to ischemia for the other) (1/8). Two out of 8 patients had an increased in anti HLA class I or II antibody titre after biopsy. Three patients did not report any clinical changes and did not show any change in lung function. A patient had a marked increase in 6-MWT from 258 m to 360 m, but only a slight improvement on Krypton SPECT-scan. No complications were observed.

Conclusions: This report shows that bronchoscopic lung volume reduction of an emphysematous native lung in single lung transplants using IBV® is feasible and seems safe, although further experience is needed.

P3076

Long-term outcome of lung recipients bridged with extracorporeal devices

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Recent evolution in extracorporeal supports allows bridging to lung or heart and lung transplant in a consistent number of cases. However, long term results of these transplants have been rarely reported. Aim of present study was to analyse early and long term results in a small n of lung transplant recipients (LTR) which have been bridged with extracorporeal devices. Nine patients (8 males, mean age39.5) have been transplanted (4SL, 2DL, 3HL). Transplant indications were: UIP (5), PAH (3), bronchiectasis (1). This latter patient (HL) died 3 days after surgery of MOF due to sepsia. 8 patients are alive at a mean of 16 months (min 3.5 - max 33). Early complications included: Re-op for bleeding (1/8) CRYMINE (5/8), slow weaning with need of tracheostomy (7/8), graft infections (1/8), acute renal failure with need for renal replacement therapy in ICU (4/8).

Medium long term complications included: AR±2 (2/8), CMV pneumo-nia/reactivation (4/8), Thrombosis (2/8), EBV related haemophagocytic syndrome (1/8); colonization with P. aeruginosa or A. fumigatus (2/8) end stage renal failure (RF) (1/8). Two of 8 patients had an increased in anti HLA class I or II antibody titres (<10%). At last follow-up visit graft function was >90% of best in 6/8 patient while 2 patients BOS-0. Mean GFR (MDRD formula) was 54ml/min range between15 and 85.

In conclusion: long term survival of ECMO bridged LTR is satisfactory, with good graft function. However, early post transplant period is almost invariably complicated by CRYMINE and slow weaning, and a high degree of chronic RF is detected.

P3077

Management of total cavitary stenoses of the trachea by replacement of trachea produced by technologies of the regenerative medicine

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Background: The use of transbronchial lung biopsy to monitor and diagnose acute cellular rejection in the lung allograft is a routine procedure in most TX centres. There is consensus in the minimum number of specimens being obtained and mostly biopsies are taken from more than one lobe. Are there differences in rejection grading at different anatomical sites? We examined our clinical data from the last 10 years to investigate the distribution of rejection grading of the lung allograft monitored by TBLB.

Methods: A retrospective study was done reviewing the pathology files and slides of TBLB performed on lung allograft recipients. In 99 patients 298 transbronchial biopsies were taken from more than one lobe and were histologically graded following ISHLT guidelines. Corresponding B scores were just available in 207 investigated cases.

Results: A-scores with identical grades were seen in 252 of 298 (85%) specimens, a single-grade difference was noted in 43 of 298 (14%) probes. Three cases demonstrated two grade differences on biopsies taken from two separate lobes (higher grade in the lower lobe). B-scores were identical in 160 of 207 (77%) specimens, a single-grade difference was noted in 45 of 207 (21%) cases. Two cases demonstrated 2 grade difference (higher grade in the lower lobe).

Among cases with different grades of A and B scores, the “lower” lobes had a higher A grade in 55% (24/46) and a higher B grade in 59% (28/47). Type of TX and underlying disease had no influence on the distribution of histological grading.

Conclusions: If limitations on the site for transbronchial biopsy exist, biopsies of the lower lobes appear more informative.

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eration which is carried out with the individual centers, except for that after this procedure the patient should receive for life immunosuppression.

Aims: To study an opportunity of use of a trachea received by methods of regenerative medicine for treatment of patients with total tracheal lesion. Materials and methods: The female 25 y.o. with complaints to constant difficulty breath, weakness, cough and endoscopy have revealed a picture of total cica-tricial lesion of trachea. Each 3-5 days patient required in bowntage of trachea. Indications to transplantation of a trachea are exposed. It was used cadaveric decellularized trachea prepared by techniques of regenerative medicine. The total resorption of a trachea was executed. Into a wall of a donor trachea are entered stem cells of the patient and factors of growth of cells. Anastomosis with own trachea were performed by vicryl 3/0. From abdomen the part of the big omentum was moved by which the donor trachea with anastomosis was completely covered.

Results: The early postoperative period was accompanied by the moderate respira-tory insufficiency, hemoptysis, expressed bronchial secretion. By the moment of discharge breath was free, a gleam of trachea on all extent was satisfactory. Patient does not require immunosuppression.

Conclusions: Regenerative medicine for preparation of the trachea with the aim of transplantation can cardinally change philosophy of thoracic surgery particularly in management of patients with total incurable stenoses of a trachea.

P3078
Benefit of pulmonary rehabilitation in candidates for lung transplantation
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Background: The benefit of pulmonary rehabilitation (PR) before lung transplant-ation (LTx) is unknown. Candidates for LTx reveal drawbacks due to chronic pulmonary diseases (COPD, interstitial lung disease (ILD), cystic fibrosis (CF), pulmonary hypertension (PH), bronchiolitis obliterans syndrome post LTx (BOS), other). Hypothesis: an 3-week PR improve functional status (forced expiratory volume in 1 sec (FEV1), vital capacity (VC), 6 min. walk distance (6-MWD), peak work load in bicycle exercise testing (PWLI), activities in daily life (ADL). Aims: to investigate the quality of life (HRQOL) (SF 36 short Form (SF)). Methods: The study included 168 patients (m/f: 74/94, age 49.4±12.0 yrs) before LTx (COPD n = 68, ILD n = 39, CF n = 27, PH n = 3, BOS n = 18, other n = 13) attended a 3 week inpatient PR. Functional status, ADL, and HRQOL (SF 36, HADS) were assessed at admission and completion of PR.

Results: (mean ± SD) 6-MWD (250±118 to 284±118 m, p < 0.001), PWLI (38±15 to 41±16 Watt, p < 0.001), ADL (96±6 to 98±5, p < 0.001) and HRQOL (all SF 36 domains and HADS (p < 0.02) but SF36 “bodily pain” (p = 0.11) improved significantly. FEV1 (30±16 to 30±16) and VC (53±19 to 53±21%) predicted) kept unchanged. Improvement in 6-MWD, PWLI and ADL was regardless of causative pulmonary disease (ANOVA p < 0.26).

Conclusion: A 3-week inpatient PR has a remarkable benefit in patients with end stage pulmonary disease awaiting LTx. Functional status and HRQOL improve significantly. Inpatient PR must be regarded as part of best practice management to optimize physical condition and mental health in candidates for LTx.

P3079
H1N1 influenza in lung transplant patients: A follow up after one year
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The 2009 outbreak of H1N1 caused significant morbidity and mortality. Long term outcome of H1N1 in lung transplant (LT) patients have not been well characterized. We did a retrospective study of LT patients diagnosed with H1N1 between July and November 2009. Data pertaining to LT, history of influenza, admission information, pulmonary function, radiograph, computer tomography scans, and echocardiograms were identified. Among 181 LT patients, there were 10 PCR confirmed cases of H1N1. Patients had a median of 4 months time since LT to infection, received immunosuppres-sive therapy, and had not received vaccination against H1N1. 60% of patients presented with fever and cough, others had non-pulmonary complaints and all received oseltamivir upon diagnosis. Consolidation was seen by imaging in 60% of patients. Median FEV1 decreased and remained low over a one-year follow up period (1.72 – 1.51 – 1.54) despite clinical improvement. Two patients progressed to really severe lung and severe LV dysfunction (EF 20-30%) despite previous LV function. These patients were on ECMO and had improvement in cardiac function and LV dysfunction. One patient died on ECMO and had severe LV dysfunction. Rapidly deterio-rated patients had developed myocardial dysfunction, but continued to decline even when this dysfunction resolved. Increased incidence of cardiac rejection and extended decreased pulmonary function is seen among LT patients infected with H1N1.

333. Epithelial cell biology

P3080
The bronchial epithelium promotes B cell survival and immunoglobulin production in a coculture system
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Background: Chronic obstructive pulmonary disease (COPD) is associated with chronic airway inflammation and structural remodelling, in particular of the epithelium, which is impaired in its capacity to transport immunoglobulin (Ig) A. Although peribronchial lymphoid follicles have been described in severe COPD, it remains unknown whether B-cell conditioning (e.g. for IgA production) is altered in this disease.

Objectives: In this study, we report on preliminary data using a model of coculture of B cells with human primary bronchial epithelial (r)differentiated in vitro in air-liquid interface.

Methods: IgA synthesis was studied in CD19+ B cells (purified by immunomag-netic sorting from healthy blood donors) following co-culture for 15 days with a bronchial epithelium. B cells were also assessed by flow cytometry for cell activation and survival (annexinV/prodipodine iodine staining).

Results: In two independent experiments, we observed that Ig production was upregulated in B cells cocultured with the bronchial epithelium, as compared to B cells cultured alone (2.2 fold increase in IgG, and modest 1.4 fold increase in IgA), whereas IgM was decreased (0.8 fold). In contrast to expression of CD69, CD80 and CD86 which did not change, B-cell survival also increased (55.3% vs 20.8% for B cells alone) following epithelial coculture.

Conclusion: These preliminary data using this model of coculture, which should reveal useful to investigate crosstalks between the epithelium and B cells with respect to COPD, confirm that the airway epithelium provides B cells with signals promoting both survival and Ig synthesis.

P3081
DUOX1-mediated hydrogen peroxide release regulates sodium transport in bronchial epithelial cells
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Clara-like H441 cells grown on non porous support form epithelial cell domes in the presence of dexamethasone. This reflects an increase in expression and activity of amiloride inhibitable epithelial sodium channels, ENaC. Dexamethasone has also been shown to facilitate the expression of NAPDH oxidase DUOX1 in lung fetal cells. We assessed the role of DUOX and subliminal (≤0.3 mM) amounts of H2O2 on both ENaC expression and activity in H441 cells. Cells forming epithelial domes induced by dexamethasone (0.1 μM, 24h) and by another differentiating agent 5-aza-2′-deoxycytidine (SAZA, 1 μM, 48h) expressed higher amounts of DUOX1 as evidenced by RT-PCR and immunocytochemistry. Dome induction by dexamethasone and SAZA can be inhibited by exogenous catalase in concentration-dependent manner (5-10 kU/ml) and by the NAPDH oxidase inhibitor diphenyl iodonium (2.5 μM), thus suggesting the involvement of H2O2. Single application of 0.2 mM H2O2 induced transient dome formation. Dexamethasone stimulated mRNA expression of all the subunits of ENaC, however this expression was not inhibited by catalase, thus suggesting that H2O2 increased only the channel activity. In patch-clamp experiments, H2O2 (0.1 mM) activated amiloride-sensitive whole-cell currents from 3.91±0.79 pA/pF to 4.76±0.98 pA/pF (p=0.01) as well as ENaC single-channel activity in cell-attached patches. These observations sug-gest that tonic production of H2O2 by DUOX1 maintains the level of vential sodium transport by lung alveolar cells. They also suggest that the upregulation of DUOX-mediated H2O2 release observed in cystic fibrosis (CF) may contribute to the hyperabsorptive epithelial cell phenotype observed in CF lung disease.

P3082
Increased expression of α1-hydroxylase (CYP27B1) in IL-13-exposed primary bronchial epithelial cells (PBEC): Consequences for activation of vitamin D and expression of the antimicrobial peptide kC-AP/IL-37
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Vitamin D (25(OH)D3) increases expression of kC-AP/IL-37 in PBEC. This requires conversion of 25(OH)D3 by 1α-hydroxylase (CYP27B1) into its active
metabolite 1,25(OH)₂D₃, that increases expression of both iCASP-18/LL-37 and the vitamin D degrading enzyme (CYP24A1). IL-13 is highly expressed in the lungs of asthmatics and low serum 25(OH)D levels were associated with lower lung function in asthmatics.

The aim of the present study was to investigate the role of IL-13 in vitamin D metabolism and to assess its effect on expression of iCASP-18/LL-37. Well-differentiated PHEC cultured at the air-liquid interface from 5 different donors were pre-incubated with IL-13 for 24 hours and subsequently exposed to 25(OH)D₃ for 48 hours to investigate CYP27B1, CYP24A1, vitamin D receptor (VDR), and its paracrine-defensive (BH2-2 and -3) and by qPCR. IL-13/18-37 expression was determined by qPCR, immunofluorescence (IF) and Western blot. Exposure of PBE to IL-13 alone increased CYP27B1 and BH3-3 mRNA (fold increases of 5.2 ± 3.13 vs. p<0.05, whereas addition of 25(OH)D₃ to IL-13 treated cells resulted in higher expression (p<0.05) of iCASP-18/LL-37 and CYP24A1 mRNA (fold increase: 72.18 and 29.9, resp.) when compared to 25(OH)D₃ alone (fold increase: 32.6 and 13.9, resp.). These results were confirmed by IF and Western blot for iCASP-18/LL-37. The present results show that IL-13 increases vitamin D metabolism in bronchial epithelial cells resulting in increased expression of iCASP-18/LL-37. Whether IL-13 can host defence against infection through this mechanism requires further studies.

P3084 Epithelial mesenchymal interactions in asthmatic children
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The alteration of the mesenchymal layer underlying the bronchial epithelium, triggered by epithelial dysfunction, is a topic of emerging interest in asthma. Whether this dysfunction is already present in asthmatic children, and therefore in the early stages of the disease, has been scarcely investigated. We evaluated the degree of epithelial damage, E-cadherin (E-cad) and TGFβ1 expression, and their relationship with basement membrane (BM) thickness in asthmatic children. Bronchial biopsies were obtained from 27 children undergoing bronchoalveolar for appropriate indications: 16 asthmatics (age 2-10yrs) and 11 nonasthmatic controls (4-9yrs). Epithelial damage and BM thickness were quantified by histochemistry and E-cad and TGFβ1 by IF and Western blot for iCASP-18/LL-37. The present results show that IL-13 increases vitamin D metabolism in bronchial epithelial cells resulting in increased expression of iCASP-18/LL-37. Whether IL-13 can host defence against infection through this mechanism requires further studies.

P3085 Increased expression of IL-19 in metabolic epithelium of patients with chronic rhinosinusitis and nasal polyps
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Chronic rhinosinusitis (CRS) is an inflammation of the nose and of the paranasal sinuses. Nasal polyposis (NP) is common in many patients with severe asthma. The pathogenesis of NP is poorly understood. The aim of the present study was to identify biomarkers for NP. We collected nasal biopsies from normal subjects without CRS (n=12), from subjects with CRS but without NP (n=10) and from patients with CRS and NP (n=10). We used Human Asthma Gene Array and real time PCR to evaluate gene expression and western blot analysis and immunohistochemistry for protein expression.

Human Asthma Gene Array showed an evident increase in IL-19 gene expression in NP from patients with CRS and NP in comparison to mucosa from inferior turbinate of normal subjects. Real time PCR confirmed the IL-19 mRNA up-regulation in patients with CRS and NP and showed an up-regulation of IL-19, at lower extent, also in the mucoea from inferior turbinate of patients with CRS in comparison to normal subjects. Western blot analysis confirmed that IL-19 is increased also at protein level in patients with CRS and NP in comparison to normal subjects. Immunohistochemistry showed that in NP IL-19 is highly expressed in the metaplastic nasal epithelium (score 4-9) when compared to normal or hyperplastic epithelium (score 1-3). When patients with CRS and NP were compared to patients with CRS or NP alone, in the absence of any other disease, no differences were observed in terms of IL-19 expression. In conclusion, the results of the present study provide compelling evidence on the putative use of IL-19 as a remodelling biomarker for identifying patients with chronic rhinosinusitis and NP.

P3086 Increased epithelial production of LPLUNC1 in cystic fibrosis lung disease
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Members of the PLUNC family of secreted proteins have been implicated in innate defence of the upper airways and nasopharynx. Although array data suggest that they are differentially expressed in some lung diseases validation has not been forthcoming. We previously showed that PLUNC1 is increased in severe cystic fibrosis (CF). In the present study we have investigated the expression of LPLUNC1 in severe CF and studied both proteins in mouse models of CF lung disease. There was marked epithelial staining of LPLUNC1 in diseased small airways and submucosal glands. In CF, similar to our previous data with SPLUNC1, the two proteins are not co-expressed in the CF lung as LPLUNC1 is co-localised with MUC5C in goblet cells, whereas SPLUNC1 is present in a non-ciliated, non-goblet cell population. Expression of both proteins was unchanged (and very limited), in CFTR knockout mice. However, in CFP-betalnα transgenic mice, a model for CF lung disease, there was strong staining of both proteins in the airways and in the luminal contents. This was most marked for lplunc1 and was noted within 2 weeks of birth. As in CF, the two proteins are present in non-ciliated cells. Expression of the putative innate immune molecules is associated with CF lung disease in both humans and mice. It remains unclear if this elevation of protein production, which results from phenotypic alteration of the cells within the diseased epithelium, plays a role in the pathogenesis of the disease.

P3087 Co-expression of LPLUNC1 and MUCSB in the bronchoalveolarized epithelium of usual interstitial pneumonia
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Idiopathic Pulmonary Fibrosis (IPF) is an irreversible and progressive lung disease with limited life expectancy after diagnosis. The cause of the condition remains elusive but it has both familial and environmental associations. Histopathological studies of IPF lungs reveal the typical "usual interstitial pneumonia" (UIP) pattern with epithelial hyperplasia, areas of scarring with fibroblast foci and characteristic morphological abnormalities, including bronchiolization of alveolar ducts, cysts and alveoli. Although it seems likely that bronchiolar abnormalities are caused by changes in epithelial cell differentiation, specific markers of this process remain elusive. By analysis of published array data sets from IPF patients, we identified LPLUNC1 as a potential candidate marker for the disease. This putative innate defence protein is normally expressed in submucosal glands (SMGs) and in a population of MUC5C+ positive goblet cells in the upper airways. Immunohistochemical analysis of lung tissue from patients with UIP revealed strong staining of LPLUNC1 within the bronchoalveolarized epithelium lining the honeycomb cysts as well as in the mucusobustance filling these regions and dispersed throughout the peripheral lung. The related protein, SPLUNC1 was not co-expressed. MUCSB was localized to the same cells as LPLUNC1, whereas MUC5C was found in goblet cells within the airways. The same pattern of staining was not seen in other chronic lung diseases, suggesting a degree of specificity for IPF. Our data support the idea that in UIP, airway epithelial cells develop characteristics of SMGs and suggest that LPLUNC1 may be a useful marker for the disease.

P3088 LSC 2011 Abstract: Differential inflammatory responses of nasal and bronchial epithelial cells to cigarette smoke extract
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Few studies compare the function of primary bronchial (PBEC) and nasal (PNEC) epithelial cells. Our aim was to compare the responses of paired PNEC and PBEC
cultures to LPS stimulation and any modulatory effects of exposure to cigarette smoke extract (CSE).

Cells, from subjects with COPD, were obtained by nasal or bronchial brushing and used at passage 3. They were stimulated for 24 h with LPS (0–25 μg/ml) pre-treatment with CSE. CSE was prepared by combusting a 12 mg tar Marlboro cigarette through 25 ml of media. Supernatants were collected and IL-8 and IL-6 measured by ELISA. The localization of TLR4 was established by FACS. For the PNEC cultures, a brief incubation with CSE (4 h) significantly inhibited LPS-induced IL-6 and IL-8 release (IL-8: 24 h treatment with 25 μg/ml LPS alone 5457±652 pg/ml and with 4 h CSE pre-treatment 3772±452 pg/ml). A more prolonged incubation with CSE (24 h) was pro-inflammatory (IL-8: 25 μg/ml LPS alone 5485±562 pg/ml and with 24 h CSE pre-treatment 7757±449 pg/ml). Although a brief incubation with CSE resulted in a lower percentage of surface and intracellular TLR4, a prolonged incubation was without effect. In contrast, both a brief and a prolonged exposure of PNEC cultures to CSE reduced LPS-induced IL-8 release (IL-8: 24 h treatment with 25 μg/ml LPS alone 5107±977 pg/ml with 4 h CSE pre-treatment 3345±609 pg/ml with 24 h CSE pre-treatment 3010±324 pg/ml), and both led to a reduced percentage of surface and intracellular TLR4. There was minimal IL-6 release from the PNEC cultures.

In conclusion, our results show that CSE are not a suitable surrogate for PNEC cultures in terms of their response to CSE/LPS combination treatment.

P3089

Cigarette smoke alters the expression of the pro-inflammatory LT4B receptor and increases the neutrophil adhesion in bronchial epithelial cells

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LTB4 is importantly involved in the inflammatory responses of chronic obstructive pulmonary disease (COPD). In COPD an increased expression of LTB4 receptors, BLT1 and of PPAR-a, was observed. Since LT4B is reduced on TLR4 mutation and since cigarette smoke extracts (CSE) increase the expression of LT4B in bronchial epithelial cells, the aims of this study were to explore whether cigarette smoke exposure (CSE) and/or cigarette smoke extract (CSE) plus an inflammatory agent (PPAR-a) BLT4 receptor. Moreover, we evaluated the effects of CSE on the expression of ICAM-1 (by flow-cytometry analysis), on the binding of ICAM-1 to ICAM-1 promoter (by ChiP analysis), and on the adhesiveness of bronchial epithelial cells to neutrophils (by flowcytometry). CSE increased the binding of ICAM-1 to ICAM-1 promoter and increased the expression of ICAM-1 in bronchial epithelial cells. CSE and mini-BAL from smokers increased the adhesiveness of bronchial epithelial cells toward neutrophils more than mini-BAL from non-smokers. These findings suggest that, in bronchial epithelial cells, CSE promote a prevalent in-duction of pro-inflammatory BLT2 receptors and activate mechanisms leading to increase neutrophil adhesion, a mechanism contributing to airway neutrophilia.

P3090

Oxidative stress induces the generation of tissue factor bearing microparticles by airway epithelial cells in vitro

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Background: Activation of the coagulation cascade is involved in the pathogenesis of pulmonary fibrosis. Although, according to the traditional view, coagulation factors present in the lung are derived from the general circulation, recent data indicate that factor (F) X is locally increased in fibrotic lung tissue in its active form. Microparticles (MP) are procoagulant and proinflammatory vesicles shed by airway epithelial cells in vitro. The generation of MP by A549 was investigated through a prothrombinase test, expressed as phosphatidylserine (PS) concentration, and a one-stage clotting assay of pro (BLT2) and anti-inflammatory (PPAR-a) LTB4 receptors. Moreover, we evaluated the effects of CSE on the expression of OCTs and their role in the pathogenesis of chronic inflammatory respiratory diseases is becoming evident. Variations in OCT expression in response to environmental insults were quantified in bronchial epithelial cells and in bronchial epithelial layers in vitro. Layers of the human cell line Calu-3 and normal human bronchial epithelial (NBE) cells showed similar OCT gene expression pattern after differentiation at an air-liquid interface for 21 days. Calu-3 layers were exposed to the aerosolized dust mice or they were physically injured in a scrape wound model. Cells were harvested after recovery for real-time PCR analysis. Significant fold-increases in the expression of OCT1, OCT3, OCTN2 and the pro-inflammatory markers CCL17 and COX-2 were measured. In “cell” western blotting, confirmed OCT up-regulation at the protein level. It was shown OCT expression in bronchial epithelial cells is enhanced after allergen and physical damage. Although further investigation into OCT functions in bronchial epithelial cells is needed, this study suggests a possible role of the transporters in the protection and regeneration of the bronchial epithelium.

P3093

Human 3D airway models to explore in vivo inhalation

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Human 3D airway models are promising models for safety and efficacy evaluation of compounds targeting the airways. The two most important reasons are (1) the models are fully differentiated and functional (incl. metabolism activity, mucus production and cilia beating) and (2) they are cultured at air-liquid interface, allowing exposure to gasses, vapours, aerosols and particles via air (relevant exposure). Healthy and diseased airway tissue (asthma, COPD) are available. Some models include cells from the upper respiratory tract (nasal tissues, larynx and trachea), where the highest impact of inhaled compounds is. We explored the use of 3D airway models, including MucAirTM, for toxicity testing, e.g. the COMET assay, cell viability and tissue and cell membrane integrity. Substances were applied as droplets. Tissue and membrane integrity of the airway models did not show an increase in COMET formation. For benzo[a]pyrene, this is likely to be related to the exposure concentration and duration. Our preliminary results indicate that the MucAirTM model system is a suitable model for safety testing, including genotoxicity and acute toxicity. In the future, we will further

P3091

Effect of cigarette smoke on protease function in alveolar epithelial cells

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Cigarette smoke is the major risk factor for chronic obstructive pulmonary disease (COPD), which accounts for several million deaths annually world-wide. The generation of reactive oxygen species (ROS) is considered to be the major contribution to smoke-induced inflammation, DNA damage and posttranslational modifications resulting in subsequent misfolding of cellular proteins. The ubiquitin proteasome system is essential for the turnover of the majority of cellular proteins. The proteasome also plays a vital role in protein quality control as it degrades abnormal and misfolded proteins, among them oxidatively-modified proteins. Conditions of massive oxidative stress, however, may result in impairment of proteasome function as ROS can directly modify the proteasome complex. In the present study, we have investigated protease function in response to cigarette smoke extract (CSE) of human and mouse epithelial cells. Treatment of these cells with CSE resulted in a time and dose-dependent increase in ROS levels. The proteolytic activities of the proteasome were also evaluated using peptide substrates. Two of the three main protease activities, namely the chymotrypsin-like and caspase-like activity, showed a time and dose-dependent alteration in response to CSE treatment. The altered proteasomal activity corresponded to accumulation of oxidatively modified and polyubiquitinated proteins. The effect of CSE on the ratio and composition of 26S and 20S proteasomes was analysed by native gel electrophoresis, immunoprecipitation and subsequent mass-spectroscopic analysis. Preliminary data indicate that posttranslational modifications of proteasomal subunits which may be responsible for the alteration of protease activity.

P3092

Variations in organic cation transporter (OCT) expression in bronchial epithelial cell layers after environmental insults

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OCTs are transmembrane carriers that mediate the transport of endogenous amines in both directions. They are essential for the preservation of several organs and have been associated with chronic inflammatory disorders like Crohn’s disease and rheumatoid arthritis. They are also dysregulated in the lung of allergic rodents after an acute ovalbumin challenge (Lips, K.S., et al. Life Sciences, 2007; 80:2263-2269). In the present study, we have investigated protease function in response to cigarette smoke extract (CSE) of human and mouse epithelial cells. Treatment of these cells with CSE resulted in a time and dose-dependent increase in ROS levels. The proteolytic activities of the proteasome were also evaluated using peptide substrates. Two of the three main protease activities, namely the chymotrypsin-like and caspase-like activity, showed a time and dose-dependent alteration in response to CSE treatment. The altered proteasomal activity corresponded to accumulation of oxidatively modified and polyubiquitinated proteins. The effect of CSE on the ratio and composition of 26S and 20S proteasomes was analysed by native gel electrophoresis, immunoprecipitation and subsequent mass-spectroscopic analysis. Preliminary data indicate that posttranslational modifications of proteasomal subunits which may be responsible for the alteration of protease activity.
assess the applicability of these models for safety and efficacy testing by exposure through the air and comparison with in vivo inhalation data. Ultimately, these models may be useful in the safety evaluation of pharmaceuticals and chemicals.

P3094

Cigarette smoke induces the release of CXCL-8 from human bronchial epithelial cells via TLRs and the induction of inflammasome

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COPD is a chronic airways diseases associated with inflammation and cigarette smoking. Airway epithelial cells are the first cells that will be exposed to cigarette smoke and are able to release CXCL-8 and IL-8. These cytokines are involved in the acute and chronic character of inflammatory processes in COPD. The aim of this study was to investigate whether Toll Like Receptors (TLRs) on human bronchial epithelial cells (HBE-140 cells) were involved in cigarette smoke-induced cytokine production.

The cigarette smoke-induced CXCL-8 production was inhibited by an antibody against TLR4 and by inhibitory ODN without CpGODN motif suggesting the involvement of TLR4 and TLR9. In addition, exposure of HBE-140 cells to TLR4 or TLR9 ligands resulted in the release of CXCL8 and IL-1β. TLR4 and also TLR9 were present on the cell surface and the expression of both receptors decreased after cigarette smoke exposure. The molecular mechanism was further investigated. It was found that the purinergic P2X7 receptors and reactive oxygen species were involved. Interestingly, the inflammasome activator monosodium urate crystals (MSU) mimicked the release of CXCL8 and IL-1β and the caspase-1 inhibitor Z-VADDCB suppressed the cigarette smoke-induced release of CXCL8. In addition, cigarette smoke, CpGODN, LPS and MSU all increased the expression of caspase-1 and IL-1β. In conclusion, cigarette smoke releases CXCL-8 from HBE-140 cells via TLR4 and TLR9 and inflammasome activation. This signal transduction pathways may contribute to cigarette smoke related diseases such as COPD.

P3095

Effect of roflumilast N-oxide on non-typable haemophilus influenzae (NTHi) interaction with human airway epithelial A549 cells

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Background/Aim: NTHi is associated with lung colonisation and exacerbations in COPD. Previously we found that NTHi invasion of airway epithelial cells is PI3-K dependent. Further NTHi survives intracellularly in vacuoles with late endosomal features, explaining airway colonisation despite NTHI-negative sputum. Here we explored whether the PDE4 inhibitor roflumilast N-oxide (RNO), the active metabolite of roflumilast (approved in EU for severe COPD), dexamethasone (DEX) and salmeterol (SAL) affect NTHi invasion of A549 cells and NTHi-induced IL-8 release.

Methods: For invasion, cells were infected with NTHi (100 bacteria/cell, 2h), incubated with gentamycin (1h) to kill extracellular bacteria, and lysed to determine intracellular bacteria by plating. Intracellular lifestyle was monitored by immunofluorescence with antibodies to late endosome markers (lamp1, CD63). PI3-K dependent Akt phosphorylation was assessed by Western. IL-8 was measured by ELISA.

Results: RNO (1μM) reduced NTHi invasion by 50% (c.f.u./well; Control: 5000±100, RNO: 2439±122, n=3, p<0.05) while DEX (1μM) and SAL (1μM) failed. Forskolin (10μM) reduced NTHi invasion by 70%, supporting a role of cAMP. RNO (1μM) curbed NTHi-induced Akt phosphorylation by 40%. Neither drug affected NTHi intracellular lifestyle. RNO (1μM) or DEX (1μM) reversed a 6.5-fold increase in NTHi-induced IL-8 release by 48.3±% and 75±% respectively and NF-κB activation.

Conclusions: PDE4 inhibition (1μM RNO) reduced NTHI internalisation in A549 cells by interfering with PI3K signalling. RNO inhibited IL-8 release. DEX, while reducing NTHI-induced IL-8, did not affect internalisation.

P3096

Glucocorticoids enhance CCL20 release in bronchial epithelial cells in a metalloprotease-dependent manner

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Glucocorticoid (GC) insensitivity is a major clinical problem in the management of asthma. Although a potential role for Th17 cells has been described in GC insensitive asthma, it is still unknown why GCs are unable to efficiently suppress Th17-mediated inflammation. CCL20 acts as a potent chemotactrant for Th17 cells. To determine the effect of GCs on CCL20 secretion and to unravel the underlying regulatory mechanisms, we examined the effect of budesonide and fluticasone (10-7-10-5M) on TNF-α-induced CCL20 and IL-8 production (ELISA and qPCR) in 16HBE human bronchial epithelial cells and primary bronchial asthma epithelium. We compared the effect of the GCs, dexamethasone (DEX, 300M) and fluticasone (PF95, 500M) with the GC receptor (GR), protein synthesis and a general metalloprotease inhibitor.

Surprisingly, we observed that GCs do not suppress, but enhance the release of CCL20 in 16HBE cells, under conditions where IL-8 was efficiently suppressed. Importantly, GCs also induced a substantial increase in the TNF-α-induced release of CCL20 in asthma epithelium. Although the TNF-α-induced CCL20 release was dependent on the ERK, JNK and STAT3 pathways, the upregulation by GCs was not blocked by their inhibition. Furthermore, our data demonstrate that the effect of GC is mediated by GR activation, which is likely mediated at posttranslational level in a metalloprotease-dependent manner.

Thus, we show for the first time that GCs enhance metalloprotease-dependent release of CCL20, which may constitute a novel mechanism of Th17-mediated GC insensitive neutrophilic airway inflammation in asthma and provide new opportunities for therapeutic intervention.

P3097

Effects of JAK-STAT inhibitors on glucocorticosteroid resistant release of CXC3 chemokines from human bronchial epithelial cells

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COPD is associated with glucocorticosteroid insensitivity. CXC3 chemokines are elevated in COPD and may drive recruitment of CD8+ lymphocytes. Expression of CXC3 chemokines is regulated by IFNγ. This study investigated the effect of JAK-STAT inhibitors PF95 and PF13 on CXC3 chemokine production from human bronchial epithelial cells. Beas-2B and primary human bronchial epithelial cells (HBEC) were pre-treated with PF95, PF13, or Dexamethasone (DEX) then stimulated with IFNγ or IFNγ+TNFα. After 24h, cytokines were measured by ELISA. Inhibition of the JAK-STAT pathway was measured by immunoblotting for phosphorylated and total STAT-1 and STAT DNA binding using Trans-AM kits. DEX had no effect on the release of CXC3.10, 10 or 11, however all were inhibited by the JAK-STAT inhibitors stimulated with either IFNγ or IFNγ+TNFα (Table 1). HBE responded similarly to Beas-2B. Both inhibitors attenuated phosphorylation level in a concentration dependent manner. DNA binding of STAT-1 and STAT-3 was inhibited but not of STAT5a or STAT5b.

Table 1. EC50 values for PF33 (nM) and PF95 (nM) on CXC3 chemokine release from bronchial epithelial cells. Mean ± SEM, n=4

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<thead>
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<th>Drug</th>
<th>Beas-2B</th>
<th>Primary</th>
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<tr>
<td></td>
<td>IFNγ</td>
<td>IFNγ+TNFα</td>
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<tr>
<td>CXC3L9</td>
<td>PF33</td>
<td>6.7±1.8</td>
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<td>PF95</td>
<td>2.1±1.5</td>
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<td>CXC110</td>
<td>PF33</td>
<td>9.5±4.2</td>
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<td></td>
<td>PF95</td>
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JAK-STAT inhibitors therefore attenuate release of CXC3 chemokines from airway epithelial cells under conditions of glucocorticosteroid insensitivity and have potential as a new anti-inflammatory treatment in COPD patients.
Corticosteroids can improve clinical outcome in patients with pneumonia. However, little is known about the effects of corticosteroids on systemic cytokine levels in these patients or which patients benefit most from corticosteroid therapy. Hospitalized, non-immunocompromised patients with CAP were randomly assigned to receive dexamethasone (5 mg once a day) or placebo. Serum levels of IL-1α, IL-6, IL-8, IL-10, IL-17, TNF-α, INF-γ, MIP and MCP were measured at various time-points during hospital stay. We enrolled 304 patients. The median level of IL-6, MCP, TNF-α, IL-1α, and IL-17, all were significantly lower (p = 0.01) on day 2 in the dexamethasone treated patients compared to the placebo treated patients. In patients with an atypical bacterium, IL-1α (p = 0.01), IL-6 (p = 0.01), IL-10 (p = 0.06) and MCP (p = 0.03) decreased faster in the dexamethasone group compared to placebo, in pneumococcal pneumonia only MCP (p = 0.07) and TNF-α (p = 0.05) decreased faster. When IL-6, IL-8 and MCP, being the most prominent proinflammatory cytokines were combined, patients who had all three cytokines above a predefined cut-off point benefited most from dexamethasone therapy. In the dexamethasone group only 2 patients (8.3%) died, while in the placebo group 8 patients (47%) died (p = 0.01).

Conclusion: Proinflammatory cytokines and chemokines decreased more rapidly in dexamethasone treated patients compared to placebo treated patients. This effect was most evident in patients with an atypical bacterium. In patients with high- risk cytokine response, dexamethasone showed a reduction in mortality and ICU admittance.

3204 Impact of bronchoalveolar lavage (BAL) multiple PCR with DNA macroarray based diagnosis on outcomes of severe pneumonia in ICU

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Objective: To evaluate BAL multiple PCR with DNA microarray (Syndrome Evaluation System, SES), Xcyton Diagnostics Pvt. Ltd., India in etiological diagnosis of severe pneumonia and its impact on outcomes.

Method: Bronchoscopic BAL in 25 (27 episodes) admission patients with severe pneumonia was tested by clinical diagnosis and SES. Empirical antibiotics were modified based on the results. Index infection, ICU, hospital and 30 day outcomes were compared with matched controls.

Results: BAL was obtained from 25 (27 episodes) study patients [mean±SD age 61.3±18.3 yrs] and 27 control patients [age 60.9±18.3 yrs]. There was no significant difference in the age (p=0.94), APACHE IV score (74.6±27.3 vs. 76.6±26.9; p=0.8) and predicted mortality (29±22.3 vs. 26.9±21.2; p=0.01). ICU length of stay (LOS) (p=0.49) and hospital LOS (p=0.73) between the groups. Mechanical ventilation was required for 26 episodes in study and 25 in controls. In the study arm all BAL were positive by SES, 9 were sterile by culture and 18 were aspirate by both methods. In SES, no MS and 4 organisms picked up by CU. In controls 7/27 BAL were sterile by culture.

In the study arm there was significantly less time to antibiotic modification (p=0.001) based on SES (31:18.4±4.4 hrs) as compared to CU (including Gram stain and colony morphology) (52±8±7.11 hrs). Observed 30 days mortality was 15/25 (study) and 13/27 (control). Index infection cure rates (p=1) and ICU (p=0.27), hospital (p=0.49) and 30 day (p=0.57) mortality were not significantly different in the two groups.

Conclusions: Multiple PCR (SES) helps in early modification of empirical therapy but shows no impact on severe pneumonia outcome.

3205 Hyaluronal infusion improves survival in endotoxic shock rats

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Background: It has been proposed that Hyaluronan (HA) acts as a vehicle for cytokines due to the strong negative charge on its surface. We hypothesized that HA would function like a cytokine scavenger, reducing inflammatory signaling cascade leading to improved survival in endotoxemia.

Methods: Endotoxin (Salmonella, 10 mg/kg) or an equal amount of 0.9% NaCl (NS) was injected into the jugular vein of rats. HA (1600 kDa, 0.35%) or NS was given 0.5 ml/kg for 3 hrs. HA or NS infusion was started at different time points; 30 min before, 1 hr after, and 4 hour after endotoxin injection. Rats were divided into control and HA groups at three different time point.

Results: The survival rate (% of rats treated with HA was higher (90%) than in controls (60%) treated with NS infusion 30 min before LPS injection; HA was higher (90%) than in controls (50%) when HA or NS infused 1 h after LPS; HA was higher (60%) than in controls (20%), when HA or NS infused 4 hours.
h after LPS. Bronchoalveolar lavage (BAL) of the animals surviving HA or NS infusion 4 h after LPS showed that total cell count and neutrophils were significantly (p < 0.01) reduced in the HA treated groups compared to controls (total cell count 1.2×10⁴/ml vs. 6.1×10⁴/ml, neutrophils 21×10⁴/ml vs. 0.2×10⁴/ml, respectively). Serum cytokines of the animals surviving HA or NS infusion 4 h after LPS showed that TNF-alpha and MIP-2 were significantly (p = 0.01) lower in the HA treated groups compared to controls (70.7 vs. 120.3 pg/ml, 1506 vs. 3459 pg/ml, respectively).

Conclusion: Continuous infusion of hyaluronan, 1600 kDa, reduced BAL cell count and serum cytokines, and improved survival in the endotoxic rats.

3206 Multi-organ failure in severe sepsis patients followed at intensive care unit: Risk factors
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Aim: We aimed to detect risk factors for mortality and multi organ failure (MOF) for patients with severe sepsis and MOF in intensive care unit (ICU).

Material-method: Retrospective data collection and prognostic cohort study. Between January 2009-March 2010 patients with severe sepsis who stayed more than 24 hours in 22 bed ICU were retrieved. Demographics, ICU severity scores (initial APACHE II, 1st and 3rd day SOFA score), use of mechanical ventilation (non invasive, invasive), sepsis agent, application of sepsis protocol, ICU length of stay (LOS), mortality were recorded. Logistic regression analysis was done for risk factors and mortality risk factors in patients with and without MOF.

Results: 347 patients (232 males) with severe sepsis were involved. Fortythree (12.4%) developed MOF and overall mortality rate was 14.9% (n=52). Presence of resistant pathogen, shock, total parenteral nutrition (TPN) and high APACHE II score were found to be risk factors for MOF (p<0.015 Odds ratio (OR) 3.47 confidence interval (CI) 1.27-9.47, p<0.000, OR:1.10, CI:1.04-1.18, respectively). Risk factors for overall mortality were presence of nosocomial infection, high 3rd day SOFA score, presence of shock, sedation and TPN (p<0.005, OR:3.39, CI:1.45-7.93, p<0.000, OR:1.51, CI:1.27-1.81; p<0.014, OR:3.24, CI:1.27-8.25; p<0.003, OR:3.64, CI:1.54-8.58; p<0.000, OR:3.38, CI:1.51-7.57, respectively).

Conclusion: In severe sepsis patients who need ICU follow up, in addition to known sepsis protocols, rational use of antibiotics and application of hospital acquired infection control programmes will further reduce MOF and mortality.

3207 Prediction of clinical severity and outcome of ventilator-associated pneumonia in a tertiary hospital using the VAP PIRO scoring system
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Background: Management and decision-making in ventilator-associated pneumonia (VAP) was commonly guided by diagnostic tools, until a recent study validated a severity assessment tool for prognostication.

Objective: To determine if VAP PIRO Scoring System can predict mortality risk compared to APACHE II.

Methods: A prospective, observational study was performed including 52 patients randomly into two groups: Group A: 32 of the patients were treated in the traditional manner using Broad spectrum antibiotics for two weeks. Group B: 46 of the patients were treated according to the new strategy (De-escalation of Antibiotics) for eight days. All patients were followed up and assessed clinically and by CPIS (Clinical Pulmonary Infection Score), at starting therapy and the days (three, eight, and fourteen) in the hospital.

Results: The proportion of patients with late and early VAP in Group A were 56.25%, 43.75% and Group B were 54.34%, 45.65%. The mortality rate was significantly higher in late and early VAP in both groups. In Group B the CPIS and clinical improvement was noticed and statistically significant in day eight, comparing to Group A (39.13%, 28.12% respectively). We studied the type of bacteria and its resistance to antibiotics, the proportion of Gram-negative almost consists two thirds in both groups with no difference in distribution of germ. The mortality rate in Group A and Group B was (65.62%, 56.52% Respectively) the difference was statistically significant.

Conclusion: The (De-Escalation of antibiotics) was possible and safe with diminution of mortality, the amounts of antibiotics used and a shorter stay in the ICU.

358. E-learning
3209 Usage patterns and feedback of online E-learning modules for “Common Trunk” trainees in medicine
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Background: - E-learning provides access after-hours for post-grad medical trainees. Learning management systems allow accurate recording of trainee activity. Aim: To observe the pattern of usage of trainees and to assess feedback on utility of online modules.

Method: A Moodle online e-learning management system – including 24 online modules, and 24 quizzes as is part of an EU funded project ESF 1.19 (malta). All 23 (14Female) “Common-trunk” trainees at Mater Dei Hospital Malta were asked to complete these modules as part of their compulsory academic activities within a 6 week deadline. Data on usage was collected by the learning management system and trainees were asked to fill in an online feedback form.

Results: All trainees (n=23) completed all modules however 36.1% of modules (M=49.8%, F=27.4%) were completed in the last week. 19 (n=21) trainees found the e-learning as a useful or very useful tool. 19(21) and 13(21) of trainees reported streamed presentations and quizzes as of good/high quality. Acquisition of new knowledge was 7.95 (SD 1.75) on as scale of 0-10. The Quality of the TT work was rated 7.97 (SD 1.75). 43.0% (M=36.6% F=7.4%) of modules were completed from 16:00-19:59, 16.5% (M=29.3%, F=16.5%), from 20:00-23:59 and 4.5% (M=8.2%, F=2.2%) from 00:00-03:59. 32.8% of modules were performed on weekends (Sat=13.6%, Sun=17.6%, AverageMon-Fri = 13.8%). Average time to complete learning module F=49.7mins, M=76.4 mins, Quizzes, F=10.1mins, M=9.5 mins.

Conclusion: Overall feedback on E-learning was positive. There was significant difference in access time and weekend use. Gender differences in time of access, and total time needed to complete modules were noted.
A questionnaire study of available sources of information regarding medical conditions and access rate in patients attending chest clinics in a district general hospital (DGH) in the United Kingdom
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Respiratory Medicine, University of Keele Medical School, Keele, United Kingdom

Background: There is increasing availability of medical information on the internet, and patients now, tend to use it more often [1,2].

Aims: To survey patients attending chest clinics (new and follow up) regarding their use of internet and other sources to access prior information about their respiratory condition.

Method: Questionnaire study of patients in respiratory clinics about the sources of information accessed by them, including internet, general practitioners (GP), other hospital consultants involved in their care, family, friends, leaflets and audio-visual media for one media period.

Results: 139 questionnaires were completed out of 161. 60 were male. Mean age was 54 (20-88).

Conclusion: The doctors remain the major source of information to the patients. However, the internet provides information to a significant proportion of our patients and this makes a compelling argument for making the internet resources more available and as reliable as possible. Our study noted that patients with cancer accessed the internet more.

References:

FeNO interpretation aid: A clinical decision support tool for interpretation of FeNO values in the patients with respiratory symptoms
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Background: Exhaled nitric oxide (FeNO) is a validated non-invasive biomarker of airways inflammation that is easy to measure, and gives immediate results. Its use has been increasing recently in routine care. Several individual factors that affect FeNO values have been identified, including age, height, weight, sex, atopy and smoking habits. These can cause difficulties in the interpretation of FeNO values.

Aims: To design and develop a Clinical Decision Support System (CDSS) that classifies the FeNO values taking into consideration the individual characteristics of a patient. Specific aims are: 1) to define the information model and specifications 2) to retrieve from published literature data to setup the knowledge base; and 3) to develop the CDSS and present a functional beta version for public evaluation.

Methods: Collaborative development with multidisciplinary meetings between healthcare professionals and computer scientists. Systematic review of factors affecting FeNO and reference values. Development of a web-based CDSS.

Results: We have outlined the model and specifications of the CDSS, including feature description, information model, taxonomic description, clinical workflow integration and software and hardware requirements. In the systematic review, 10 studies met the selection criteria and were used to form the datasets for the Knowledge Base of the CDSS. A web-based CDSS, that is compliant with common standards, was developed using HTML, PHP, Javascript and CSS.

Conclusion: The CDSS was successfully developed, based on the best available medical knowledge, and is accessible online for testing at http://feno.med.up.pt.

Conclusion: The pollen diary allows patients suffering from allergic rhinitis due to pollen to correlate the type (conjunctival, nasal, bronchial) and severity (degree 0–3) of her symptoms and the type and frequency of medication to correlate with the kind and intensity of the pollen exposure at the place of her stay.

The symptoms are entered daily in an online form by the patient anonymously. The pollen exposition for the user is investigated with the help of the postcode, and the suitable data from the area’s pollen trap are correlated with the symptoms and medication. Because pollen data are collected eurowide and stored in a common database (EAN, Vienna) it is possible to correlate the pollen load and symptoms of the affected person even if that person was travelling (in Europe). The user can chart symptoms and pollen flight and interpret accordingly.

The pollen diary is retrievable under www.pollendstuf.gen and www.pollendiary. free of charge and exists to date (1.2.2011) in 9 languages. In 2009 >4 000 and in 2010 >10 000 patients have used it.

The pollen diary supports the diagnosis of pollinosis and might be of help for therapy evaluation. It is appropriate for application in clinical studies on immunotherapy or for the effect of drug therapies. Also, this instrument is able to determine individual threshold values for pollen concentrations inducing sympoms and is likely to determine the clinical meaning of pollen kinds which were considered up to now not enough.

Furthermore any change of the threshold values is documented with these tools in the population throughout Europe and is measured.

Internet-based self-management (IBSM) in asthma, from evidence to practice: A qualitative study of barriers and facilitators for implementation
Johanna L. van Gaaalen1, Jiska B. Sneek-Ströband1, Leti Vo1,2, Mirta J. Bakker1, Ad A. Kaptein2, W.J.J. Assendelft3, Luuk N.A. Willems4, Bart P.A. Thomsen1, Jacob K. Sønn1, The IMPASSE (IMPLEMENTation Strategies of Internet-Based Asthma Self-Management Support in Usual care) Study Group: 1 Medical Decision Making, Leiden University Medical Center (LUMC), Leiden, Netherlands; 2 Medical Psychology, LUMC, Leiden, Netherlands; 3 Public Health and Primary Care, LUMC, Leiden, Netherlands; 4 Oto-Rhino-Laryngology, Medical Faculty University of Vienna, Vienna, Austria; 5 Primary and Community Care, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Background: Internet-Based Self-Management (IBSM) support cost-effectively improves asthma control, asthma related quality of life, number of symptom-free days and lung function in patients with mild to moderate persistent asthma [Nasinde Meier 2009]. The current challenge is to implement IBSM in current clinical practice.

Methods: We conducted focus groups (FG) and interviews (for those not being able to participate in focus groups) based on a theoretical model. 20 patients (PT), 17 general practitioners (GP) and 8 practice nurses (PN) participated in FGs. In each FG an average of four persons participated. PTs (18-50 yr) had mild to moderate persistent asthma (>3 months ICS in the past year). Interviews were conducted with 2 PTs, 5 PNs and 4 GPs. FGs and interviews were audio-taped, fully transcribed and coded independently, using an existing framework of barriers [Grol 2004].

Results: Main barriers at patient level: unawareness of the level of asthma control, asthma was not perceived as a chronic condition, PTs experienced difficulty of...
395. Important new developments in paediatric respiratory physiology

3216 Micron-sized particle deposition in the developing rodent lung
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Conclusion: Our findings indicate that future implementation strategies for IBSM need to address relevant barriers at professional/organisational and patient level, i.e. assessment of the level of asthma control and integration within daily practice.

3217 Newborn airway compliance is correlated with amniotic fluid soluble leukocyte-associated Ig-like receptor-1 (LAIR-1)
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1Pediatrics, University Medical Center Utrecht, Utrecht, Netherlands; 2School of Women’s and Children’s Health, University of Queensland, Brisbane, Australia

Hypothesis: High amniotic fluid sLAIR-1 is associated with normal newborn airway function and low infant airway morbidity.
Methods: In a healthy birth cohort, 152 newborns underwent lung function measurement. Amniotic fluid was collected during labour and sLAIR-1 was measured. To determine whether amniotic fluid sLAIR-1 could be spill-over from the neonatal circulation, cord blood and amniotic fluid sLAIR-1 were measured in parallel. At age 1 month, airway compliance and resistance were assessed with the single occlusion technique. Wheeze during follow-up was determined using a parental log.

Results: sLAIR-1 was detected in all amniotic fluid samples. Airway compliance and amniotic fluid sLAIR-1 were positively correlated (p=0.2,9, P=0.001). This correlation did not change by adjustment for sex or maternal smoking. Resistance was not correlated. Amniotic fluid sLAIR-1 was lower in children who wheezed at ages 6 and 9 months (P=0.04 and 0.05). Cord blood and amniotic fluid sLAIR-1 concentrations were not correlated.

Conclusion: The association between amniotic fluid sLAIR-1 and newborn airway compliance underscores the long-term clinical impact of intra-uterine immune activation.

3218 Elicitability of defensive reflexes within the breathing cycle
Silvia Varchova, Bruno Demoulin, Mathieu Boussels, Cyril Schweitzer, Bruno Chenuel, Anne-Laure Leblanc, Françoise Marchal. Laboratoire de Physiologie, Faculté de Médecine, Vandœuvre-lès-Nancy, France

Background: Both the cough (CR) and the expiration reflex (ER) are usually elicited within prolonged (more than 10 s) mechanical stimulation. The use of a discrete mechanical stimulus (150 ms) has shown that the type of response is strongly dependent on the phase of the breathing cycle. CR is favoured in inspiration (I) and ER in expiration (E). The observation suggests that CR and ER exhibit different regulatory mechanisms, but it still remains unclear which mechanisms control the expression of these responses.

The aim of the study was to assess the elicibility of CR and ER in relation to the timing of stimulation within breathing.

Methods: 313 mechanical stimulations of the trachea were performed in 14 rabbits using stimuli lasting 50 to 600 ms. CR and ER were identified from airflow and tidal volume. The timing of the stimulus was defined within TI and TE arbitrarily divided into 4 equivalent epochs (TI1 to TI4 and TE1 to TE4) and expressed as percentage of TI and TE of the reference breath.

Results: CR incidence during TI increased from 43% in TI1 to 56% in TI4. CR was almost absent in TE1 (4%) and whenever observed, always preceded by ER. In TE2-4, CR incidence increased, e.g., 50% in TI, to a nadir of 75% at TE4, i.e., the transition from TE to TI. On the contrary, incidence of ER increased throughout inspiration (from 15% in TI1 to 54% in TI4), and further to 54% in TE1. The incidence then decreased gradually from 33% in TE2 to 19% in TE4.

Conclusions: Elicitability of CR and ER exhibit a completely different pattern within each phase of breathing suggesting implication of distinct control mechanisms in their regulation and/or different impact of inputs from lung afferents in the timing of the CR and ER.

3219 Increased fetal growth protects against early wheeze, airway hyper-responsiveness (AHR) and current asthma in early mid-childhood: Results from the Raine birth cohort
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Reduced fetal growth has been associated with increased wheeze and atopy and decreased lung function in young children. This analysis of the Raine longitudinal birth cohort aimed to examine the impact of fetal growth on asthma, lung function and AHR outcomes at 6 and 14 years of age.

Methods: The Raine birth cohort enrolled women prior to 18 weeks gestation to standard (18w; n=1419) or intensive (18w, 24, 28, 34 & 38w; n=1415) ultrasound monitoring groups. Children were re-assessed at 1, 2, 3 yrs with further respiratory assessments at 6 and 14 yrs. Composite data on 1174 children are included in this analysis. Conditional fetal growth centiles were derived for head circumference, femur length and abdominal circumference. Impact of fetal growth on early wheeze (wheeze at 1, 2 or 3 yrs), current asthma, spirometry or AHR at 6 or 14 yrs was assessed using generalised estimating equations with time as repeated measures.

Results: Measures of increased fetal growth throughout pregnancy were significantly associated with a reduced risk of early wheeze, AHR at 6 yrs and current asthma at 14 yrs (p<0.05). In addition there was a tendency for increased FEV1, predicted at 6 and 14 yrs and FEV1/FVC at age 6 and 14, although these relationships were not significant.

Conclusions: In agreement with previous reports we have demonstrated increased fetal size reduces the risk for wheeze in early life. The current data suggests that the impact of fetal programming on lung health extends into early adolescence and further reinforces the need for further research to discover how fetal growth may be optimised.
Results: The drop in R at 4 Hz (R4) with increasing age was linearly related to the magnitude of R4 at 4 years of age (Pearson’s correlation coefficient of 0.87 and 0.88 at baseline and after bronchodilatation, respectively). Interestingly, the slope characteristicizing this relationship was almost similar for the baseline (0.75) and the postbronchodilator values of R4 (0.81). Division of the group of children based on the magnitude of R4 at 4 years revealed that the change in R4 with increasing age was not related to differences in growth rate (see figure). Although the differences in R4 in 4-year-old children disappeared to a large extent with the increase in age, the subgroups of children still had significantly different R4 values by the age of 9 years.

Conclusion: Four-year-old children with high airway resistance exhibit the largest drop in resistance with growth to 9 years of age; this drop in resistance is independent of airway muscle tone at young age.

Multicentre feasibility and variability of measuring the lung clearance index in healthy volunteers

Susanne Fuchs1, Helmut Eilmann2, Johannes Eder3, Uwe Mellies4, Jörg Gross-Oetternbach5, Burkhardt Tümmler6, Doris Shaba, Andrea Jobel7, Matthias Greise6, Jan Ripper4, Ernst Rietschel7, Susanne Zeidler7, Frank Ahrens8.

In healthy volunteers

The Lung Clearance Index (LCI) is superior to spirometry in detecting early lung disease in Cystic Fibrosis and correlates with structural changes seen on CT-scans. The LCI has the potential to become a novel outcome parameter for clinical and research purposes. Longitudinal studies are required to further prove its prognostic value. Multi-centre design is likely to facilitate realisation of such studies.

Therefore, the aim of the present study was to assess multi-centre feasibility and inter-centre variability of LCI measurements in healthy children and adolescents. Measurements were performed using the EasyOne Pro, MBW module (ndd, Switzerland) by 8 participating CF centres. Marien Hospital Wessel, Wels, Germany; 2Department of Paediatric Cystic Fibrosis Centre, Medical University Innsbruck, Austria; 3Pneumologische Poliklinik, Medical University Essen, Essen, Germany; 4Pneumologische Poliklinik and Neonatologia, Medical University Hannover, Hannover, Germany; 5Pneumologische Poliklinik and Allergology, Charité Berlin, Berlin, Germany; 6Dr. von Haemmerzehl Kinderspital, Medical University Munich, Munich, Germany; 7Cystic Fibrosis Centre, University Hospital of Cologne, Cologne, Germany; 8Cystic Fibrosis Centre, Children’s Hospital Hamburg Altona, Hamburg, Germany

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Methods: Impedance spectra were obtained in 760 healthy children (335 male), aged 2-13 years and with height 90-160 cm using a commercial forced oscillation device (FOT) device (I2M, Chess Medical, Belgium). AX between 6 Hz and the resonant frequency was calculated in 647 children. Backward stepwise linear regressions identified anthropometric predictors of AX, and z-score equations were generated. Absolute and relative changes in AX post bronchodilator were calculated in 496 children.

Results: AX was predicted by height (p<0.001) and sex (p=0.004). Both absolute and relative changes in AX to bronchodilator were dependent on baseline lung function and height. A significant BDR using AX was defined as a decrease in absolute or relative AX of 33.2 kU/L and 8%, respectively.

Conclusions: We have provided healthy reference ranges for AX to aid in disease diagnosis, and defined cut-off values for a positive BDR by AX.

360. New insights in the incidence, variation and risk factors of asthma

Ike-breaking abstract: Association of asthma with IgE to Staphylococcal enterotoxins in a GA2LEN population based case-control study

Peter Tomassen1, Claas Bachert1, Peter Burney2, Deborah Jarvis3, on behalf of the GA2LEN Survey Follow-Up Working Group.

Introduction: Presence of specific immunoglobulin E for staphylococcal enterotoxins (SE-IgE) in serum has been associated with severe asthma and nasal polyposis, but the prevalence and link to asthma in the general population has not been studied. We aimed to determine the prevalence of serum SE-IgE and to study the association with asthma in the general population.

Methods: The GA2LEN Survey Follow-Up group conducted a multi-centre case-control study in 18 centers across Europe. Subjects were sampled from a preceding cross-sectional survey in 4 groups (controls, at-risk asthmatics, chronic rhinosinusitis subjects, and those having both). Subjects answered questionnaires, underwent spirometry and skin prick testing for common allergens, and serum SE-IgE was measured. Analyses were weighted for sampling, using inverse probability weights.

Results: 3505 subjects participated, of which 2908 in 15 centers provided complete information and blood samples. The weighted overall prevalence of asthma was 10.6%, and the prevalence of SE-IgE >0.10 kU/L was 29.3%. SE-IgE was significantly associated with the presence of asthma, adjusting for age, sex, allergy and smoking history. The strength of the association was dependent of the SE-IgE concentration (odds ratio 1.01; 1.33; 1.54 in the first, second and third tertiles).

The association was not modified by the presence of a positive skin prick test or tobacco smoking.

Conclusion: Presence of IgE to Staphylococcal enterotoxins is highly prevalent, and is associated with asthma in the general population across Europe. These findings open perspectives on a role for bacterial superantigens in the pathogenesis of asthma.

3224 Asthma incidence in a national sample of Canadian adolescents

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Background: Estimates of asthma incidence and its determinants have rarely been obtained from rural regions, especially in adolescent populations.

Objective: To compare the incidence of asthma among Canadian adolescents in rural and urban regions and to examine the determinants of asthma incidence.

Methods: We used data from the National Population Health Survey (NPHS), a nationally representative longitudinal survey of Canadians. The NPHS uses a complex survey design with data collected every 2 years since 1994/95. The NPHS collects information on socio-demographics and some health behaviours. All persons aged 12-18 years without asthma in Cycle 1 were followed until a reported diagnosis of asthma or censoring up to Cycle 7. Rural residence was defined by living in an area of <1000 people and ≥400 people/km². Incidence and Cox regression analyses were population weighted and bootstrapping procedures were used to estimate variances.

Results: This sample represented 2,482,610 adolescents of whom 293,445 developed asthma. Approximately 19% of the cohort was rural living at baseline. The incidence of asthma was approximately 10.2 per 1000 person-years and was higher in...
urban dwellers than rural dwellers (10.9 vs. 7.7 per 1000 person-years). In adjusted analysis, rural residence was not associated with asthma development [Hazard ratio (HR) = 0.58, 95% CI = 0.25-1.32, p = 0.19]. Being female and being exposed to passive smoking were both associated with the development of asthma (p < 0.01).

Conclusions: Unlike results from younger children, a rural dwelling was not protective of developing asthma among adolescents, despite showing a trend. Asthma prevention initiatives for adolescents should target girls and focus on smoking exposure.

3225
Temporal patterns of wheeze during the school ages in a population-based cohort
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Introduction: Wheeze, as suggestive of asthma, may follow various time courses during childhood. Incidence, remission and relapse rates are high. Compared to the pre-school ages, school age and adolescence have been less studied. The aim was to characterize temporal patterns of wheeze in school children.

Methods: At age 7-8 years, 3,430 (97% of invited) children in Northern Sweden completed ISAAC questionnaires. The same questions were used in 10 yearly follow-ups until age 17-18. Data from the 2,622 (76.4%) subjects that participated at 5 or more occasions were analysed.

Results: From age 7-8 to 17-18 one third reported wheezing at some occasion. Persistent wheeze from age 7-8 was reported by 2.9%. It was closely associated with rhino-conjunctivitis and parental asthma at age 7-8, RR 10 (6.6-15) and 5.3 (3.5-8.2). Incident wheeze persisting until age 17-18 was reported by 7.6%, while 2.6% had remitted wheeze, i.e. wheeze at age 7-8 but not at study end. Remitted wheeze was associated with respiratory infections before age 7-8, RR 4.1 (2.2-7.8). Transient wheeze for 1 year or more, not persisting until age 17-18, was seen in 8.7%. Of the 12.0% reporting intermittent periods of wheeze with no clear pattern, nearly half wheezed only at 1 or 2 occasions.

Discussion: In this large cohort of school children followed yearly by questionnaires, the majority of children with any wheeze during the school years were neither wheezing at age 7-8, nor at age 17-18. Half of the children wheezing at age 7-8 were in remission by age 17-18. Whereas wheeze associated with respiratory infections has a good probability of remission, heritability and concomitant allergic rhinitis predict persistence of wheeze.

3226
Seasonal variations in asthma attacks and grass sensitisation
Cristina Canova, Peter Burney, Deborah Jarvis, on behalf of the European Community Respiratory Health Survey I. Respiratory Epidemiology and Public Health, NIHR, Imperial College, London, United Kingdom
Seasonal variation in asthma mortality and hospitalization has been reported. In this study we describe seasonal variation in asthma symptoms and assess whether this was modified by SPT sensitisation. Asthmatics aged 20-44 years (n=3253) taking part in the European Community Respiratory Health Survey I are included. Participants identified bi-monthly periods they usually experienced attacks of asthma. Effect modification of sensitisation to grass, cat, dust, birch. Alternaria on asthma attacks in each bi-monthly period was assessed within each country, using marginal logistic regressions, based on generalised estimating equations. Interaction coefficients were then combined using random effects meta-analysis. Seasonal variation in asthma attacks was seen in most countries, although with different patterns. Seasonal variation was not modified by sensitisation to indoor allergens (cat, dust) but was modified by sensitisation to grass.

Figure 1 Grass bi-months interaction risk of an asthma attack

In Southern Europe the risk of asthma in May/June compared to Jan/Feb in those with IgE to grass was six times that seen in asthmatics not sensitised to grass. Overall sensitisation to Alternaria increased the risk of attacks in Jul/Aug compared to Jan/Feb (OR 2.3).

Asthma sensitised to grass and Alternaria experience seasonal exacerbations likely triggered by allergen exposure. The effect of pollen on asthma severity in a sub group of susceptible asthmatics may be much greater than previously documented.

3227
Initiation of controller medication in newly diagnosed asthma patients: Impact on economic resource utilization
Pierrick Bedouch1, Mohsen Sadatsafavi1, J. Mark FitzGerald2, Carlos Marras3, Larry Lynd1, 1Collaboration for Outcomes Research & Evaluation (CORE); 2Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; 3Department of Medicine & Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada
Introduction: To better understand the economic burden of asthma, we compared asthma-related direct costs among adults prescribed controller regimens.

Methods: A cohort of newly diagnosed asthma patients (14-65 yrs), initiating a controller therapy for the first time between 1997 to 2007, was created from the health administrative database of British Columbia, Canada. Five cohorts of patients were created according to the controller prescribed (i.e. inhaled corticosteroid (ICS group), ICS-long-acting beta-agonist combination (ICS-LABA group), ICS+LABA in separate formulations (ICS+LABA group), leukotriene receptor antagonist (LRA group) or ICS+LRA in separate formulations (ICS+LRA group)). Index Date (ID) was defined as the date controller medication prescribed. Direct cost of asthma in the post-ID year (2008 Canadian dollars) was calculated from the hospital, physician visits, and prescription records, adjusted for multiple imputations, estimated from the pre-ID year.

Results: 153,224 patients were included: 109,601 ICS, 34,184 ICS/LABA, 2,249 ICS+LABA, 6,289 LRA; 901 ICS+LRA. The average age was 37.7 and 61.0% were female. The average direct costs of asthma for the post-ID year for the ICS group was 265.2$. All other groups had higher incremental costs: ICS/LABA $315.9, ICS+LABA $218.2, LRA $198.4, and ICS+LRA $372.4 (all p<0.01). Older age, higher resource, and higher cumulative dose of rescue medication use in the pre-ID year were predictors of resource use in the post-ID year (p < 0.01).

Conclusions: Initiation of ICS, as recommended by guidelines, was associated with the lowest costs than initiation of other controller or combination therapies.

3228
A longitudinal study investigating factors associated with changes in lung function over time in early life (age 3 to 11)
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Background: Previous studies have investigated factors associated with poor lung function in children. However, these studies use a cross-sectional approach which ignores changes in lung function over time. In this study, we develop multilevel longitudinal models in order to investigate factors affecting developmental change in lung function in early life.

Methods: In a population-based birth cohort 1185 participants were recruited pre-natally and followed prospectively (1, 3, 5, 8 and 11 years). At each time point, a validated questionnaire was administered to collect information on asthma-related symptoms, height and weight. We assessed atopy and lung function (Specific Air- way Resistance (sRaw), plethysmography) at each follow-up. We use a longitudinal mixed models approach to determine predictors of change in sRaw over time.

Results: Univariate longitudinal analyses revealed marked deterioration in sRaw among children who were atopic (mean difference 2.85%, 95% CI 1.05%-9.84%, p=0.003). Children who wheezed also had poorer lung function (mean difference 5.20%, 95% CI 0.87%-2.54%, p=0.01). Boys had poorer lung function compared to girls (mean difference 3.48%, 95% CI 0.87%-6.52%, p=0.03) and also had a higher rate of deterioration of sRaw over time which increased by 0.011 units (p=0.012) per year. In a multivariate longitudinal model, the factors which best predicted diminished lung function were atopy, increased BMI, paternal atopy, gender and current wheeze.

Conclusion: Multilevel longitudinal models allow us to predict factors associated with diminished lung function as well as factors associated with change in lung function over time.

3229
Transforming growth factor beta-1 gene polymorphisms and course of asthma
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TGFβ1 is a cytokine with a potent role in asthma, in particular in airway remod-
eling. We investigated the role of TGFβ1 gene single nucleotide polymorphisms (SNPs) in the course of asthma. Four haplotype tagging SNPs (rs7254679, rs4803455, rs1880469, rs1047924) were genotyped in 215 asthmatics with a 30-year follow up (population 1) and in 99 asthmatics who provided bronchial biopsies (population 2). Associations of SNPs with lung function, bronchial hyperreactivity (BHR i.e. PC20≤16mg/ml), complete remission (pro bronchodilatation FEV1% predicted > 80% & absence of BHR, symptoms, medication), baseline membrane (BM) thickness and number of submucosal vessels were investigated using linear or logistic regression. Associations of SNPs with baseline serum 25-hydroxyvitamin D [25(OH)D] levels and adult-onset asthma. Serum 25(OH)D were not independently associated with adult-onset asthma.

Conclusions: Baseline serum 25(OH)D level was not associated with the risk of asthma in either unadjusted or adjusted models. Second, we performed the stratification analysis by BMI. In men, the OR was 2.12 (95% CI 0.93-4.80) and 1.38 (95% CI 0.77-2.47) for BMI < 25 and BMI ≥ 25, respectively. In women, baseline serum 25-hydroxyvitamin D [25(OH)D] levels were not independently associated with adult-onset asthma.

Serum 25(OH)D were not independently associated with adult-onset asthma.

Conclusions: Baseline serum 25(OH)D level was not associated with the risk of asthma in either unadjusted or adjusted models. Further adjustment for body mass index (BMI) yielded an OR of 1.47 (95% CI 0.93-2.32). In women, baseline serum 25-hydroxyvitamin D [25(OH)D] levels were not associated with the risk of asthma in either unadjusted or adjusted models.

Serum 25(OH)D were not independently associated with adult-onset asthma.

Conclusions: Baseline serum 25-hydroxyvitamin D [25(OH)D] levels were not independently associated with adult-onset asthma.

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Serum 25(OH)D were not independently associated with adult-onset asthma.
broblast differentiation markers in control fibroblasts. IFP fibroblasts were less sensitive to cycloamine treatment. Though, addition of recombinant SHH had no effect.

Conclusions: Our results show that the signaling pathway downstream of SHH is activated in IFP. SHH activity is also necessary to TGF-β induced myofibroblast differentiation. These data support a pro-fibrotic action of the SHH pathway in IFP.

3234

Heat Shock Protein 27 modulates mesothelial and epithelial to mesenchymal transition (EMT)

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Introduction: Pulmonary fibrosis (PF) has currently no treatment. We have shown that adenoviral gene transfer of TGF-β1 (AdTGF-β1) to the pleura induces a severe pleural fibrosis that invades the paranchyma. In this process, mesothelial cells differentiate into myofibroblasts (α-SMA positive cells) through an EMT-like process suggesting a key role of mesothelial cells in PF. Heat Shock Protein 27 (HSP27), is a chaperon for actin. Its role in fibrogenesis is unknown.

Methods: Sprague Dawley rats received intrapleural injection of AdTGF-β1 or AdDL (empty vector). Mesothelial Met-5A and A549 cells were treated with rTGF-β1.

Results: In vitro: 1) mesothelial cells are susceptible to rTGF-β1 induced EMT 2) HSP27 is strongly linked to α-SMA during EMT (colocalisation and co-immunoprecipitation). 3) HSP27 overexpression induces an EMT and α-SMA mediated HSP27 inhibition blocks TGF-β1 induced EMT and mesothelial cell migration 4) HSP27 modulates the TGF-β1/MAPK pathway. Data were reproduced in A549 epithelial cells.

In vivo: 7 days after AdTGF-β1 injection, HSP27 and α-SMA are overexpressed and localized in alveolar and septal wall areas. AdTGF-β1 rats treated by intrapleural injections of OGX427 (Antisense Oligonucleotide, ASO, directed against HSP27) have a strong decrease in HPS27, α-SMA expression, mesothelial cells migration into the paranchyma and fibrosis compared to AdTGF-β1 rats treated with control ASO.

Conclusion: HSP27 plays a major role in EMT and could be a key target to inhibit EMT in PF and others diseases involving EMT. This work was supported by: 1 – the EU, 7th FP, HEALTH-F2-2007-202224 eurIPFnet – La “Recherche en santé Respiratoire” et la Société de Pneumologie de Langue Française

3235

Long-term effect of hepatocyte growth factor in the normal lung: A stereological assessment

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Background: Hepatocyte growth factor (HGF) gene transfer attenuates bleomycin induced lung fibrosis. Being a multifunctional pleiotropic factor, HGF is a potent mitogen for alveolar epithelial cells and shows antiapoptotic properties. Thus, we hypothesize that HGF might lead to remodelling processes within the alveolar walls in normal rat lungs.

Material and methods: Adult male Fisher rats F344 were instilled with 350 μg bleomycin in saline. One month after HGF gene transfer, animals were sacrificed and the total volume of interstitial cells and basement membrane within the septal walls. An emphysema-like phenotype was not observed.

Conclusions: Our results show that the signaling pathway downstream of SHH is activated in IFP. SHH activity is also necessary to TGF-β induced myofibroblast differentiation. These data support a pro-fibrotic action of the SHH pathway in IFP.

3236

HGF expressing stem cells in the human fibrictic lung originate from the bone marrow

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Background: Pulmonary fibrosis (PF) is a progressive disease of unknown etiology. Abnormal alveolar epithelial wound repair after injury may result in pulmonary fibrosis. We hypothesize that stem cells have a healing capacity by migrating to the site of injury and secreting hepatocyte growth factor (HGF) which supports alveolar epithelial repair, therefore contributing in reduction of fibrosis.

Methods: Immunohistochemistry using paraffin lung sections from patients with two histological lung fibrotic pattern, usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) (both n=5) was performed with several stem cell markers.

Results: Specific cells in the lung parenchyma were stained positive for HGF in UIP and NSIP. They were mainly located in the fibrotic areas. These HGF-positive cells did not co-stain for markers of alveolar epithelial cell (Surfactant protein C) or mesothelial cells (vimentin). However, HGF-positive cells showed strong co-staining for the mesenchymal stem cell markers CD44, CD29, CD105, and CD90, indicating that HGF positive cells in the lung are of stem cell origin. The HGF-positive cells were also positive for CXXCR4, suggesting that the HGF-positive cells in UIP and NSIP are recruited from the bone marrow.

Conclusion: HGF-positive stem cells with the origin of the bone marrow (CXXCR4 positive) can be detected in both UIP and NSIP, indicating a crucial role in the development or resolution of pulmonary fibrosis. These data indicate a possible role for stem cell therapy patient with fibrictic lung disease in the future.

362. Obstructive sleep apnoea in children and adults

3237

Late-breaking abstract: Cardiac function in a revascularized coronary artery disease cohort with obstructive sleep apnoea with and without daytime sleepiness in the RICCADA trial

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Objectives: The RICCADA study is a randomized, controlled trial started in 2005 addressing the impact of CPAP in revascularized coronary artery disease (CAD) patients and concomitant OSA (Apnoea-Hypopnoea-Index [AHI]≥15) without daytime sleepiness (Epworth Sleepiness Scale <10). The primary outcome is the combined rate of new revascularization, myocardial infarction, stroke and cardiovascular mortality over a mean period of 3 years. Among secondary outcomes, cardiac function is also evaluated.

Participants and methods: Among 660 screened CAD patients, 511 (399 OSA, 112 non-OSA) have been assessed by echocardiography and p-NT proBNP at baseline.

Results: Compared to non-OSA subjects, patients with OSA had thicker interventricular septum and left ventricular posterior wall, enlarged left atrium and more diastolic dysfunction. Left ventricular ejection fraction was similar (56.9 vs 58.3%, p=0.040). The primary outcome was the combined rate of new revascularization, myocardial infarction, stroke and cardiovascular mortality over a mean period of 3 years. Among secondary outcomes, cardiac function is also evaluated.

Conclusions: In this RICCADA cohort, adverse alterations in cardiac structure as well as diastolic dysfunction were more common and p-NT-proBNP values increased in OSA patients compared to non-OSA patients. Whether the more elevated p-NT-proBNP values in the non-sleepy subjects reflect a poorer prognosis and if CPAP is effective in OSA patients remain to be demonstrated when the trial is completed.

3238

Feasibility of implanted upper airway nerve stimulation therapy to treat obstructive sleep apnea

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We studied a second generation Upper Airway Stimulation system (Inspire Medical
Methods: Twenty children (mean age 6.3±3.2, M/F:12/8, with referred OSAS, underwent urinary collection at the morning after the polysomnography, sleep questionnaire, medical examination. 8-Isop was assessed in urinary sample.

Introduction: Prevalence of sleep disordered breathing (SDB) in middle-aged general population was reported to be around 9% of women and 27% of men in studies performed in the 80’s-90’s. Considering the recent improvements in the sensitivity of recording techniques, our aim is to revaluate the prevalence of SDB in the general population.

Methods: 505 subjects (47.1% women, 50.3±5.6 y.o. BMI 25.7±4.4 kg/m²) participating in an ongoing population-based cohort study (HypnoLaus, Lausanne, Switzerland) underwent complete polysomnographic recordings at home and had an extensive clinical workup including Epworth Score (ESS). Prevalence of SDB was determined according to apnea-hypopnea index (AHI) using two different scoring criteria: AASM 1999 and 2007.

Results: With AASM 2007 criteria, prevalence of SDB with AHI thresholds of 5/h, 15/h and 30/h was 45.7%, 15.7% and 6.3% respectively in men and 11.9%, 2.5% and 0.8% respectively in women. Mean ESS score was 11.9±4.0 in men and 8.7±4.9 in women. Prevalence of SDB with ESS≤10 was 12.0%, 6.7% and 2.6% in men and 5.5%, 2.1% and 0.4% in women.

Conclusion: In HypnoLaus population-based study, prevalence of SDB is higher than previously reported, especially in middle-aged men. This appears to be due to differences in scoring criteria and to a higher sensitivity of nasal pressure sensors compared to thermocouple.

3242 Morbidity prior and after a diagnosis of sleep disordered breathing. A controlled national study

Poul Jenum, Jakob Kjellberg, Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Center for Healthy Aging, Faculty of Health Sciences, University of Copenhagen, Glostrup Hospital, Copenhagen, Denmark Danish Institute for Health Services Research, DSI, Copenhagen, Denmark

Background: Sleep disordered breathing (SDB) causes significant burdens. Most studies have focused on cardiovascular diseases (CVD) after a diagnosis of sleep apnea (SA) or obesity hypventilation syndrome (OHS) but the overall morbidity prior to a SDB diagnosis is incompletely evaluated.

Methods: Using data from the Danish National Patient Registry (1999-2006), we identified all national patients with a diagnosis of SA (19438), or OHS (755). For every patient, we randomly selected 4 age-, sex- and socioeconomic-matched citizens from the Danish Civil Registration System Statistics. We further extracted information from the Danish Ministry of Health, Danish Medicines Agency, and National Health Security

Results: Pts with SA and OHS presented increased morbidity (p<0.01) up to more than eight years prior to a SDB diagnosis of SA the most common contacts were diseases of the endocrine, nutritional and metabolic diseases (Odds Ratio (OR) SA/OHS 4.5/4.8), nervous system; OR 4.4/5.5), respiratory system (OR 2.9/4.0), skin and subcutaneous tissue (OR 2.5/1.3), infections (OR 1.8/3.0), CVD (OR 1.7/1.3), genito-urinary system (OR 1.3), ear-nose and throat (OR 1.3), psychiatric diseases (OR 1.1/1.4). After a SDB diagnosis, patients also presented significant morbidities and mortality. CPAP treatment reduced mortality (6.6% versus 5.5 in non-SAP pts, 4.0% in control subjects).

Conclusion: Patients with SDB shows significant morbidities several years prior to...
Obstructive sleep apnea and hypopnea syndrome (OSAHS) is characterised by sleep-disordered breathing and daytime sleepiness. The Epworth Sleepiness Score subjectively quantifies sleep propensity whilst the Apnoea-Hypopnoea Index (AHI) is an objective value for the severity of OSAHS. An audit was undertaken to test whether standards held true regarding OSAHS remain so in a Gloucestershire population. Firstly, that mean ESS varies between patients and partners according to their perceptions of patient sleep propensity. Secondly that there is no correlation between patient ESS and AH1 and a weak correlation between partner perspective ESS and AHI as shown by previous studies. The audit also aimed to test whether severity levels of ESS were found to be independent of severity levels of AH1 when the data were placed in severity categories according to guidelines.

During the audit, 40 sets of patient-partner data were collected retrospectively from a sleep database and analysed. It was found that there was no mean difference between patient and partner perspective ESS scores (p=0.906), disputing the first standard. The partner perspective ESS (r=0.464), but not the patient ESS (r=0.305) correlated with AH1 therefore the second standard held true. An additional test found that severity levels of ESS were independent of severity levels of AH1 both for patient and partner scoring. ESS was found to be a poor predictor of AH1. To improve this, an alternative questionnaire was devised which combines subjective and objective risk factors for OSAHS. Evaluation of this questionnaire requires stratification.

### 3244

**Long-term follow-up of severe obstructive sleep apnea-hypopnea syndrome**

**Methods:** We prospectively followed 589 consecutive patients (pts) with clinically suspected OSA. The pts were included and followed-up for a mean period of 7 years by sleep questionnaires, antropometric measurements, polysomnography and questionnaires. The structure of the study population according to European Society of Hypertension 2007 Guidelines: from the 59% of pts with SI 11% with normal values, 15% stage I, 24% stage II, 8% stage III. AHI in all 3 levels, with reference normal, is extremely significant (p<0.001) in hypertensive patients. Only severe OSA is the strongest predictor for hypertension, OR 3.2 (p<0.001 CI 1 1-6 5 59). Mild and moderate OSA did not significantly influence the appearance of SH (p<0.014, OR 0.58, CI 0.29 1.20, p=0.24, CI 1.52, CI 0.76 2.86). SH is a weak predictor for OSA in univariate analysis, p=0.045, OR 1.76, CI 1.01 3.08.

**Conclusions:** Patients with OSA are exposed to a higher risk of developing SH. A strong predictor for SH is only severe OSA.

### 3245

**Can the Epworth sleepiness score predict the apnoea-hypopnoea index in obstructive sleep apnoea and hypopnoea syndrome?**

**Results:** According to the BQ, 24 patients (38%) scored a low risk of OSAS and 39 patients (62%) scored a moderate to high risk. The BQ scores averaged 7.9 (49 mmHg). A high-risk ESS scores averaged 7.9 (49 mmHg). Sensitivity of the BQ was 67% and specificity 48%. The internal consistency of the BQ ranged from moderate to good (Cronbach’s α 0.61-0.80). Sensitivity and specificity of the ESS were 45% and 81% with a cut-off point of 8, which according to literature, is the cut-off point between normal and abnormal sleepiness. A cut-off point of 5 appeared to be a more preferable choice for this population. Sensitivity increased to 71% and specificity decreased to 48%. Internal consistency of the questionnaires was good (Cronbach’s α 0.80).

**Conclusion:** Given the low to moderate sensitivity and specificity, the BQ and ESS were found to be of low value as screening tools for patients who referred to the sleep clinic.

### 3246

**Berlin questionnaire and Epworth sleepiness scale, useful screening instruments for obstructive sleep apnoea syndrome?**

Anamnie Mensink, Steven Ull, Bert Kuipers. Pulmonary Department, Isala Klinieken, Zwolle, Overijssel, Netherlands

**Methods:** Conceived a retrospective validation study for the Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS). 63 patients completed these questionnaires prior to their first outpatient visit to our sleep clinic. All patients underwent a polysomnography to determine their Apnea-Hypopnea Index. Diagnosis was based on the anamnesis and the polysyrgy results. Sensitivity, specificity and internal consistency of these questionnaires were assessed.

**Results:** According to the BQ, 24 patients (38%) scored a low risk of OSAS and 39 patients (62%) scored a moderate to high risk. The BQ scores averaged 7.9 (49 mmHg). Sensitivity of the BQ was 67% and specificity 48%. The internal consistency of the BQ ranged from moderate to good (Cronbach’s α 0.61-0.80). Sensitivity and specificity of the ESS were 45% and 81% with a cut-off point of 8, which according to literature, is the cut-off point between normal and abnormal sleepiness. A cut-off point of 5 appeared to be a more preferable choice for this population. Sensitivity increased to 71% and specificity decreased to 48%. Internal consistency of the questionnaires was good (Cronbach’s α 0.80).

**Conclusion:** Given the low to moderate sensitivity and specificity, the BQ and ESS were found to be of low value as screening tools for patients who referred to the sleep clinic.

### 3247

**Randomized trial of 6 auto-adapting CPAP devices**

Sara Neale, Fiona Buchanan, Nicola Allouat, James R. Catterall, Adrian H. Kendrick. Sleep & NIV Unit, University Hospitals Bristol, Bristol, United Kingdom

Auto-adapting CPAP (aCPAP) is used to manage patients with obstructive sleep apnoea (OSA). Different suppliers use different algorithms. We have compared 6 commercial devices - ResMed S8, Breas PV10, Weinmann Somnosmart, Goodbreath Autopilot, Devilbiss Auto LT, Respironics M-series. Patients had used fixed pressure CPAP for 6+ months before the study and had good compliance. Each aCPAP device was used for 2 weeks in a randomized order. Data from the second week was analyzed and included CPAP use (hours), 7 day sleep diary card (SDC), and patient preference. The SDC included scores for Sleep Quality Exercise Level (Excellent to Poor), Awakenings (0 to 6+) and a 100mmVAS (0=Aleep,100=Drowsy). 23 patients were enrolled, 15 completed. Mean±SD weight - 117±8.29 kg, age - 57±11yrs and 4% diprate 27±1%. If patients could not tolerate the aCPAP device, they used their fixed pressure device. There were significant differences between devices.
We conclude that auto-CPAP devices have different outcomes and patient preferences. This may affect adherence to treatment for OSA in short-term trials.

3248

Randomized trial of 6 auto-adapting CPAP devices: Effects on quality of life
Sara Neale, Fiona Buchanan, Nicola Allaouat, James R. Catterall, Adrian H. Kendrick. Sleep & NIV Unit, University Hospitals Bristol, Bristol, United Kingdom

Auto-adapting CPAP is used to manage patients with obstructive sleep apnoea, with suppliers using different algorithms. We have compared 6 devices - ResMed S8, Breas PV10, Weeminn Somnosmart, Goodnight 420E, Devilbiss Auto LT, Respironics M-series. Patients were all using a fixed pressure (FP) device for at least 6 months before the study and had good compliance. Each device was used for 2 weeks, in a randomized order. Data from the Epworth Score (ESS), SF-36 and the Multidimensional Fatigue Inventory (MFI-20) was obtained at the end of each 2 week period. If the patient was unable to use a CPAP device, the highest score representing the biggest effect on quality of life (QoL) was used. 23 patients were enrolled, 15 completed. Data was analysed using repeated measures ANOVA and are shown as mean (95% CI).

Result: We conclude that the choice of auto-adapting CPAP device may have a significant impact on QoL, certainly in the initial stages of adaptation to this treatment.

3249

Transcutaneous measurement of pCO2 (ptcCO2): Time delay from change in alveolar pCO2 to first response in ptc CO2
Nils Henrik Holmehald1, Jon Andrew Hardie2, Ove Fondevæde1, Ivar Ellingsen1
1Respiration Physiology Lab, Glitråklinikken, Hakadal, Akershus, Norway; 2Internal Medicine, Haukeland University Hospital, Bergen, Hordaland, Norway

Introduction: The ptcCO2 delay has been estimated to 16 sec (healthy subjects) [1] and >60 sec (hypercapnic patients) [2]. We simultaneously record polysomnography (PSG) and ptcCO2 from COPD patients and needed the response time in our setup.

Material: 9 stable COPD patients (6 male) with mean FEV1 41% of pred. (SD 20).

Method: Patient in supine position wearing face mask connected to a stopcock, inlet selecting either room air or a bag with 4% CO2 in air. pCO2 measured by Radiometer TOSCA 500, probe on the earlobe. Arterial samples from arterial catheter analyzed by Radiometer ABL 500. 3 test-phases, each 200 sec: 1) stable phase breathing room air, 2) increasing phase after switching to 4% CO2, 3) decreasing phase after switching back to room air. TOSCA pCO2 was read every 0.5 sec for 120 sec, then every 10 sec. Arterial samples were drawn 3 times during phase 1), every 5 sec the first 30 sec of phase 2) and 3), then every 30 sec for a total of 150 sec.

Results: First response time (T0) meaning time from change in alveolar pCO2 to ptcCO2 > 2SD off stable phase.

Mean T0 (SD in increasing phase: 54 (5.6) sec.

Mean T0 (SD in decreasing phase: 57 (15) sec.

For arterial pCO2: 13.3 (5.6) sec and 11.7 (2.5) sec, accordingly.

Conclusion: Scoring pCO2 from COPD patients, the transcutaneous pCO2 signal should be left-shifted 2 epochs (1 minute) as a respiratory event changing alveolar pCO2 will show a first ptcCO2 response after 54-55 sec.

References:

Figure 1

Conclusion: Early use of CPAP via mask therapy had better outcomes to post surgical atelectasis especially with smoker and elderly patients.
364. Physical activity monitors: from toy to valid tool?

3.253 Validity of 6 activity monitors during standard physical activities in COPD – Comparison with indirect calorimetry

Vogini Raste1, Daniel Langer2, Chris Burtin3, Ioannis Vogiatzis4, Santiago Giavedoni4,barry Anderson5, Nicholas Hopkinson1, Ioannis Vogiatzis4, Barry Peterson5.

Background: Reduced physical activity is an important feature of COPD. A range of monitors are available, but the validity of their various output parameters is not well established for patients with chronic diseases. The IMI PROactive project evaluated 6 activity monitors: SenseWear (SW); Actiwatch (AW); Actigraph (AG); Dynaport Minimod (MM) and Lifecorder Kenz (KZ).

Methods: 40 patients (GOLD stage 1-4; Age 67 ± 10 years) were recruited in 4 centres. Patients wore all activity monitors and a portable metabolic system and performed a 1 hour standard activity set (including 40 patients (GOLD stage 1-4; Age 67 ± 10 years) were recruited in 4 centres. Patients wore all activity monitors and a portable metabolic system and performed a 1 hour standard activity set (including walking, standing, stair climbing and upper limb tasks). Activity intensity (METs), assessed by indirect calorimetry, was compared to activity monitor outcomes. Average VO2 during the protocol was also calculated (8.78 ± 2.60 ml/kg/min) and compared to activity monitor outputs. METs (SW, MM); activity counts or Vector Magnitude Units, VMU (AW, AG, RT3); or a general activity outcome tool?

Table 1

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Patients wearing monitor</th>
<th>Overall monitor score (0-100)</th>
<th>No technical problem (%)</th>
<th>No interference in daily life (%)</th>
<th>Willing to wear over 1 week</th>
</tr>
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<tbody>
<tr>
<td>AW</td>
<td>31</td>
<td>93*</td>
<td>94</td>
<td>84</td>
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<tr>
<td>KZ</td>
<td>33</td>
<td>90*</td>
<td>97</td>
<td>85</td>
<td>82</td>
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<tr>
<td>RT3</td>
<td>28</td>
<td>90*</td>
<td>93</td>
<td>79</td>
<td>74</td>
</tr>
<tr>
<td>SW</td>
<td>56</td>
<td>86*</td>
<td>90</td>
<td>79</td>
<td>83</td>
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</tr>
<tr>
<td>MM</td>
<td>37</td>
<td>74*</td>
<td>81</td>
<td>54</td>
<td>73</td>
</tr>
</tbody>
</table>

p-value 0.05 NS 0.06 NS

*pGroup similar results ANOVA.

Conclusion: All monitors showed good overall acceptance ranging from 74% (MM) to 93% (AW). The lower overall score for the MM suggests that potentially the position on the back of patients is perceived less comfortable. EG is a fellow of UEFR-UFSCar/Brazil. PDEE CAPES

3.255 Accuracy of three activity monitors in patients with COPD – Validation by video

Mikael Andersson1,2, Charlotte Urell1,2, Margareta Emtner1,2.

Introduction: COPD patients have a slowing of movements due to muscle disuse, muscle wasting and increased dyspnea. The use of walking aids such as rollators are common. Slow movements, low movement intensities and the use of rollators might occur when used in patients with severe COPD.

Aims and objectives: To assess the accuracy regarding number of steps from three AM’s when used in patients with severe COPD.

Table 1

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Patients wearing monitor</th>
<th>Overall monitor score (0-100)</th>
<th>No technical problem (%)</th>
<th>No interference in daily life (%)</th>
<th>Willing to wear over 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>AW</td>
<td>31</td>
<td>93*</td>
<td>94</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>KZ</td>
<td>33</td>
<td>90*</td>
<td>97</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>RT3</td>
<td>28</td>
<td>90*</td>
<td>93</td>
<td>79</td>
<td>74</td>
</tr>
<tr>
<td>SW</td>
<td>56</td>
<td>86*</td>
<td>90</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>AG</td>
<td>31</td>
<td>86*</td>
<td>97</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>MM</td>
<td>37</td>
<td>74*</td>
<td>81</td>
<td>54</td>
<td>73</td>
</tr>
</tbody>
</table>

p-value 0.05 NS 0.06 NS

*pGroup similar results ANOVA.

Conclusion: All monitors showed good overall acceptance ranging from 74% (MM) to 93% (AW). The lower overall score for the MM suggests that potentially the position on the back of patients is perceived less comfortable. EG is a fellow of UEFR-UFSCar/Brazil. PDEE CAPES

Results: Table 1 gives median (IQR) for Pearson correlation between VO2 and activity monitor outcomes and that between mean METS over the study and mean activity monitor output.

Conclusion: The MM, SW, RT3 and AG give acceptable estimates of minute-by-minute variation in metabolic activity during physical activity. SW, MM, AW and KZ show acceptable correlations between overall metabolic activity and monitor output. These findings could guide users in choosing valid activity monitors for research or clinical questions.
the upper arm). Activities included walking at different speeds, walking with a rollator, walking in stairs, sitting, lying, or eating. As criterion validity, video recording and manual step count was used.

Preliminary results: Significant differences (p < 0.05) in the number of steps detected by AM’s compared to manual step count was found (Table 1).

Conclusions: Caution in interpreting results from activity monitoring seems warranted if the outcome is number of steps derived from different AM’s. The SenseWear Armband seem unsuitable for detecting number of steps in severe COPD, especially if a rollator is used.

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Energy expenditure during daily activities as measured by two motion sensors in patients with COPD

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Background: In patients with chronic obstructive pulmonary disease (COPD), energy expenditure (EE) assessment during the performance of daily activities is not yet studied in depth. The aim of this study was to determine which daily activities are more demanding to patients with COPD and to compare the accuracy of EE estimation given by the pedometer Digiwalker SW701 (DW) and the multisensor SenseWear Armband (SAB).

Methods: Thirty-six patients with COPD (20 men; FEV1 48 ± 18.8% predicted; BMI 25.7 ± 8.1 kg/m2) were submitted to a modified version of the Glitlre ADL-test, which included five activities performed for one minute each: walking on the level, walking on the level carrying a backpack, walking up/downstairs, rising/sitting in chairs and moving objects in and out of a shelf. During the protocol subjects wore both devices concomitantly, and indirect calorimetry (IC) was simultaneously performed as the criterion method to assess EE. The most demanding daily activity for individuals with COPD was performed as the criterion method to assess EE.

Results: A factorial analysis of variance for daily activities revealed that up/downstairs, rising/sitting and rising on chairs are more demanding to patients with COPD and IC. The SAB underestimated EE in comparison with IC by 3.7 ± 2.5 (P < 0.05). EE estimation by the SAB did not show difference in comparison with IC for the other tasks; p > 0.05. EE estimation given by the pedometer Digiwalker SW701 (DW) and the multisensor SenseWear Armband (SAB) are more demanding to patients with COPD and the accuracy of EE estimation given by the pedometer Digiwalker SW701 (DW) and the multisensor SenseWear Armband (SAB) are not statistically significant differences.

Conclusion: Walking up/downstairs was the main energy-demanding activity for patients with COPD. Furthermore, during daily activities, the multisensor showed adequate overall estimation of energy expenditure, as opposed to the pedometer.

3257

Dyspnea and fat free mass are major determinants of reduced physical activity in COPD patients

Francesco Costa, Gianna De Cusatis, Laura Malagrino, Sandra Antonelli, Claudia De Simone, Sabrina Santerini, Barbara Vagaggini, Pierluigi Paggiaro, Francesco Costa, Gianna De Cusatis, Laura Malagrino, Sandra Antonelli, Claudia De Simone, Sabrina Santerini, Barbara Vagaggini, Pierluigi Paggiaro, Francesco Costa, Gianna De Cusatis, Laura Malagrino, Sandra Antonelli, Claudia De Simone, Sabrina Santerini, Barbara Vagaggini, Pierluigi Paggiaro, Francesco Costa, Gianna De Cusatis, Laura Malagrino, Sandra Antonelli, Claudia De Simone, Sabrina Santerini, Barbara Vagaggini, Pierluigi Paggiaro

Background: Physical activity is reduced in patients with chronic obstructive pulmonary disease (COPD), and this has been associated with systemic inflammation and left cardiac dysfunction (Magnussen et al, AJRCCM 2008) to assess the predictors of physical activity, expressed as daily steps, in COPD patients.

Subject and methods: In a cross sectional study 45 COPD (FEV1%: 52 ±17.1, 34 male) underwent: physical activity evaluation by Armband (as a mean of a 7-day monitoring period), pulmonary function tests (PFT), cardiopulmonary exercise test (CPET) with assessment of dynamic hyperinflation, arteral blood analysis, SaO2 monitoring period), pulmonary function tests (PFT), cardiopulmonary exercise test (CPET) with assessment of dynamic hyperinflation, arteral blood analysis, SaO2

Results: Multivariate linear regression analysis stepwise method were performed using daily steps as dependent variable. The severity of dyspnea (MRC) and the free fat mass (FFM%) explained 43% of the variance of the physical activity, while other physiologic and biologic markers did not have additive effects.

Conclusion: Dyspnea and nutritional status are extra-pulmonary parameters that play a relevant role in the limitation of the physical activity level in COPD patients.

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Smoking, exercise capacity and physical activity in daily life in physically independent elderly

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Background: Smoking results in cardiovascular changes that can lead to a gradual decrease in exercise capacity and, when associated with the physiological changes related to the aging process, can decrease the physical performance of the elderly.

Objective: To investigate the relationship between smoking, exercise capacity and physical activity in daily life (PADL) in physically independent elderly.

Methods: Two hundred and nine physically independent elderly with normal lung function were assessed. They were distributed into four groups: smokers (SG; n=12; 6 women, 66 [64-71] yrs, BMI 24 [21-28] kg/m2), ex-smokers (ESG; n=65; 31 women, 69 [64-74] yrs, BMI 27 [25-31] kg/m2), passive smokers (PSG; n=42; 36 women; 66 [63-70] yrs, BMI 28 [25-31] kg/m2) and nonsmokers (NSG; n=92; 69 women, 67 [64-71] yrs, BMI 28 [24-32] kg/m2). Subjects were submitted to assessment of exercise capacity (6 minute walking test [6MWT]) and the incremental shuttle walk test (ISWT), PADL using a questionnaire (Baekte) and a step counter, as well as smoking habits.

Results: There was no statistically significant difference among groups regarding functional and maximal exercise capacity and PADL, as seen in table 1.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>SG</th>
<th>ESG</th>
<th>PSG</th>
<th>NSG</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT (% pred)</td>
<td>90 [79-104]</td>
<td>93 [85-102]</td>
<td>92 [84-98]</td>
<td>97 [90-107]</td>
<td>0.06</td>
</tr>
<tr>
<td>SAB</td>
<td>1.8 to 4.2</td>
<td>7Kcal</td>
<td>17.1, 34</td>
<td>3258</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Physically independent elderly with preserved lung function, smokers or not, seem to present similar pattern of exercise capacity and PADL.

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Activity outcomes correlation of 6 monitors in COPD, a field study part of the PROactive project

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Background: Monitoring Physical activity (PA) in COPD patients is a new out- come to assess effects of interventions. It is unknown to what extent outcomes of different Physical activity monitors (PAM) interrelate when used in patients with COPD, especially if a rollator is used.

Aim: To assess the predictors of physical activity, expressed as daily steps, in COPD patients using daily steps as dependent variable.

Results: Multivariate linear regression analysis stepwise method were performed using daily steps as dependent variable. The severity of dyspnea (MRC) and the free fat mass (FFM%) explained 43% of the variance of the physical activity, while other physiologic and biologic markers did not have additive effects.

Conclusion: Dyspnea and nutritional status are extra-pulmonary parameters that play a relevant role in the limitation of the physical activity level in COPD patients.

The most demanding daily activity for COPD patients (Age 68[65-71] years, BMI 27[25-31] kg/m2) was performed as the criterion method to assess EE. The most demanding daily activity for individuals with COPD was performed as the criterion method to assess EE.

Results: A factorial analysis of variance for daily activities revealed that up/downstairs, rising/sitting and rising on chairs are more demanding to patients with COPD and IC. The SAB underestimated EE in comparison with IC by 3.7 ± 2.5 (P < 0.05). EE estimation given by the pedometer Digiwalker SW701 (DW) and the multisensor SenseWear Armband (SAB) are more demanding to patients with COPD and the accuracy of EE estimation given by the pedometer Digiwalker SW701 (DW) and the multisensor SenseWear Armband (SAB) are not statistically significant differences.

Conclusion: Walking up/downstairs was the main energy-demanding daily activity for patients with COPD. Furthermore, during daily activities, the multisensor showed adequate overall estimation of energy expenditure, as opposed to the pedometer.
Introduction: A group of 18 well-controlled asthmatic patients were evaluating bronchial biopsies for asthma to extreme altitude.

Methods: Symptoms, spirometry and FeNO values were obtained before, during and after the climb (up to 5600 m of altitude). Pre BD FVC was measured and cells from the lower airways were obtained by sputum induction before and after the expedition. mRNA was isolated, CDna was prepared and RT-PCR was used to measure sputum mRNA quantities as described.

Results: During the expedition there was a decrease in FVC and FVC which reached a maximum at 4300 m. The pre BD FVC (% predicted) was significantly decreased when measured after the expedition as compared to baseline measurements before the expedition (6.6%, p=0.004). FeNO values were not different between the different time points (p=0.17). Decreased asthma control was observed after the expedition as assessed by asthma control questionnaires (p=0.002). Sputum neutrophil percentages were significantly higher after expedition compared to before the expedition (p=0.04). Concomitantly, sputum IL-17 mRNA was increased after the expedition as compared to before expedition (p=0.007). A correlation of serum Clara Cell protein 16 and sputum IL-17mRNA was found (r=0.57, p<0.001).

Conclusion: Asthma patients have slightly worse lung function and asthma control after climbing to extreme altitude. Increased signs of neutrophilic inflammation were found in the airways as represented by higher sputum IL-17 mRNA and neutrophils.

Assessment of airway neutrophil activation in adult non-essential asthma

Results: Only one asthmatic individual in our study was neutrophilic (>61% neutrophils). The neutrophil has been proposed to be a principal cell type involved in non-essential asthma (NEA).

Background: It is now evident that there are different pathophysiology underlying different asthma phenotypes. The neutrophil has been proposed to be a principal cell type involved in non-essential asthma (NEA).

Aims: To investigate different aspects of neutrophil activation in NEA.

Methods: 24 adult asthmatics (9 eosinophilic asthma (EA)±2% sputum eosinophils), 15 NEA) and 18 healthy controls were recruited by advertisement and successfully underwent clinical assessment, spirometry and sputum induction. Sputum was analysed for neutrophil number (differential cell count), levels of neutrophil-associated soluble mediators (myeloperoxidase (MPO), IL-8 and MPP-9, by ELISA) and neutrophil expression of CD11b (flow cytometry).

Results: Our study indicates the role of adenosine regulation of DC’s differentiation in BA. The heterogeneity in responses to AdoR’s stimulation may be due to two groups of individuals characterized by high and low response to AdoR’s stimulation. We identified that 50% of individuals with BA and 16% of healthy volunteers demonstrated high responsiveness to NECA.

Conclusion: Our study indicates the role of adenosine regulation of DC’s differentiation in BA. The heterogeneity in responses to AdoR’s stimulation may be used as a basis for individual BA treatment development.
tion of corticosteroids and cold bronchial hyperresponsiveness (CBH) in patients with bronchial asthma (BA).

Aim: To determine the role of target-cells sensitivity to corticosteroids in cold bronchial hyperresponsiveness development in BA.

Methods: 44 patients with BA were recruited. The mean level of asthma control was 18.6±1.0 points (Asthma Control Test). The absorption of cortisol by blood lymphocytes (ACL) in the standard test “in vitro” with hydrocortisone before 3-minute isocapnic cold air (<20°C) hyperventilation (ICAH) was studied. CBH was diagnosed by the drop of FEV1 after ICAH (ΔFEV1)<10% from initial value. Researches of the patients were divided into two groups: the 1st (28 patients) was with constant values of hormone absorption by lymphocytes, the 2nd (16 patients) had lower values. ACL values were (0.701±0.054) x 10^3 mg/kg/1000 cells and (0.527±0.038) x 10^3 mg/kg/1000 cells, respectively (p<0.01). CBH was found out in 22 patients of the 1st group and in 6 patients of the 2nd one (χ^2=7.42; p<0.01).

In the 1st group there was the biggest part of patients (87%) with a high degree of CBH (ΔFEV1<18.5%) and a mean level of CBH (ΔFEV1), within the range of 14.2±18.4%. The 2nd group had only low values of CBH (ΔFEV1), within the range of 10.0-14.1%. The risk of high degree of CBH in patients of the 2nd group was three times higher than in the 1st group: chances ratio was 3.45; 95% confidence interval 1.28-9.4.

Conclusion: CBH in BA patients is associated with the decrease of transmembrane penetration of glucocorticoids into target cells.

P3265

LSC 2011 Abstract: Effect of inhaled apocynin on reactive oxygen species concentration in exhaled breath condensate of asthmatics
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Reactive oxygen species (ROS) have a strong impact on homeostasis and are thought to play an important role in inflammation in asthma. The sources of oxidative stress in patients with chronic inflammatory lung diseases derive mainly from increased amount of ROS and reactive nitrogen species (RNOS), generated by airway cells. Apocynin is an agent which blocks NAPDH oxidase - the enzyme, responsible for ROS production. The anti-inflammatory activity of apocynin has been postulated in the majority of cell lines and animal models of inflammation. Therefore, considering apocynin activities, we investigated the effect of nebulized apocynin in 14 nonsmoking asthmatics, in placebo-controlled, cross-over design study. Effects of apocynin have been checked 30, 60 and 120 minutes after nebulization with inhaled breath condensate (EBC) samples. Additionally, we investigated safety parameters. Apocynin significantly decreased H2O2 concentration in EBC in comparison to placebo after 60 and 120 min. (0.29 ±0.05 μM vs. 0.03 ±0.04 μM, respectively). Moreover, apocynin significantly reduced NO2 concentration 30 and 60 min after nebulization (2.75 μM vs. 4.65 μM, and 2.5 μM vs. 4.05 μM, respectively) in comparison to placebo. Finally, apocynin caused a significant decrease of NO concentration in EBC after 60 and 120 min after administration, comparing to placebo (5.34 μM vs. 8.2 μM (60 min), and 5.3 μM vs. 8 μM (120 min) respectively). No influence of apocynin on safety parameters, and no adverse effects has been observed.

These data suggest that using apocynin might be a promising solution to alleviate inflammatory process, and probably, symptoms of inflammatory diseases.

P3266

Quantitative proteomics on bronchial biopsies from asthma and COPD: Effects of budesonide treatment
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The global proteome of individual bronchial biopsy material from asthma and COPD patients has not been fully ascertained. The aim was to determine if mechanisms of disease and responses to treatment can be detected in biopsies from patients with asthma and COPD, using a quantitative proteomics technology. Endobronchial biopsies, pre and post treatment, were taken from patients with asthma (n=12) and COPD (n=11), as well as non-smoking (n=3) and smoking (n=7) healthy controls. Patients were randomised to double blind treatment with either placebo or budesonide (800 μg daily for 3 months). Quantitative proteomics technology was used to identify and quantify biopsy proteins. Pathways analysis was performed using Bioinformatics software. A total of 1937 proteins were identified from all subjects. Proteome differences had lower values. ACL values were (0.701±0.054) x 10^3 mg/kg/1000 cells and (0.527±0.038) x 10^3 mg/kg/1000 cells, respectively (p<0.01). CBH was found out in 22 patients of the 1st group and in 6 patients of the 2nd one (χ^2=7.42; p<0.01).

In the 1st group there was the biggest part of patients (87%) with a high degree of CBH (ΔFEV1<18.5%) and a mean level of CBH (ΔFEV1), within the range of 14.2±18.4%. The 2nd group had only low values of CBH (ΔFEV1), within the range of 10.0-14.1%. The risk of high degree of CBH in patients of the 2nd group was three times higher than in the 1st group: chances ratio was 3.45; 95% confidence interval 1.28-9.4.

Conclusion: CBH in BA patients is associated with the decrease of transmembrane penetration of glucocorticoids into target cells.

Lipoxins (LXs) are biologically active eicosanoid possessing anti-inflammatory properties. Lipoxin A4 (LXA4) signaling blocks asthmatic responses in human and experimental model system. There are evidences that respiratory diseases, including severe asthma, display defective release of lipoxin signals. To assess the role of pro- and anti-inflammatory mediators in airway homeostasis of asthmatic children, we examined the levels of LXA4 and leukotriene (LT) B4, a potent neutrophil chemotaxant, in the induced sputum supernatants (ISs), from intermittent (IA) and moderate (MA) asthmatic children treated with high doses of inhaled corticosteroids (ICSs), and control children (C). In order to address whether LXA4 and glucocorticoids have overlapping role in the resolution of inflammation, we evaluated the effect of LXA4 treatment on glucocorticoid receptor (GR) phosphorylation, in the presence or absence of LXA4 receptor (FPRL-1/ALXR) blocking peptide, in peripheral blood neutrophils (PBN) from C, using both Western Blot and Flow cytometry analyses. We found that LXA4 was higher in ISs from IA compared with MA and C, while LT-B4 was inversely correlated. In addition, we showed that LXA4 induced GR phosphorylation (Ser211) via ALXR in PBN from C, since the use of the receptor blocking peptide reversed the effect of LXA4. Our findings provide evidences for the hypothesis that a defective generation of anti-inflammatory LXA4, associated with an increased LT-B4 production, may be involved in a reduced ability of the ongoing ICS therapy in the control of airway inflammation in children with MA.

P3267

The interplay of LXA4 and glucocorticoid receptor-based mechanisms in airway inflammation of childhood asthma
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Allergic disorders, such as asthma, are symptomatic reactions of the immune system to common and innocuous environmental antigens. These inflammatory disorders are caused by aberrant immune regulation in which various signalling receptors are involved. Pathogen recognition receptors linked to transcription factors families of receptors are one of the key components of the innate immune system. The function of these receptors has been linked with susceptibility towards the development of allergic diseases, including asthma, making the TLRs and NLRs good targets for novel effective therapies of allergic diseases. In this study the mRNA expression levels of different TLRs and NLRs in the lung tissue in mild and severe mouse models of allergic asthma were measured by q-PCR. In addition, broncho-alveolar lavage fluid (BALF) was collected and cell numbers analysed. The mild and severe asthma models different TLR and NLR mRNA expression profiles are observed. In the severe asthma model, a higher cell influx in BALF is seen. Moreover, a significant correlation is found between the mRNA expression of TLR3, TLR6 and TLR9 and the total cell number in the BALF.

P3269

Mesenchymal stem cells down-regulate inflammation but not airway hyperresponsiveness in experimental asthma
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Introduction: Mesenchymal stem cells (MSCs) have immunomodulatory properties. MSCs may have a potential to down-regulate airway inflammation in asthma, but may as well serve as building blocks for unwanted airway remodeling. Here we tested the effect of MSCs in experimental asthma.

580s
P3270

Aerobic exercise reduces allergic airway inflammation and remodeling by deactivating airway epithelial cells and leukocytes

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The regular practice of aerobic exercise (AE) has been shown to reduce chronic allergic airway inflammation and remodeling (CAAIR), but the mechanisms involved remain poorly understood. In the present study we investigated if 4 weeks of AE deactivates airway epithelium and peripheral leukocytes in a model of CAAIR. Thirty-two animals were divided in control, aerobic exercise, ovalbumin and ovalbumin+aerobic exercise groups. Mice sensitized (10ug/mouse, days 0, 14, 28 and 42) and challenged with ovalbumin (200 μg) on day 42, were submitted to AE (21st until 50th day, 60min/session; 5x/week). The results demonstrated that AE in OVA-sensitized mice significantly reduced eosinophils in BAL and in airway wall and also the accumulation of collagen fibers on airway wall. This anti-inflammatory and anti-fibrotic response induced by AE in sensitized animals was followed by reduced expression of the followings markers by airway epithelial cells and also by peribronchial leukocytes: IL-4, IL-5, IL-13, CCL11, CCL5, VCAM-1, iNOS, NF-kB, GP130, 3- nitrotyrosine, 8-isoprostane, IGF-1, EGRF, VEGF, TGF-beta, MMP-12 and TIMP-2 (p<0.01). AE in sensitized animals also increased the expression of anti-inflammatory cytokines IL-10 by leukocytes and airway epithelial cells. Taken together, these results demonstrate that the beneficial effects of AE on allergic airway inflammation and remodeling is a multifactorial response involving deactivation of airway epithelial cells and also of leukocytes, by inhibition of Th2 response, chemokines, adhesion molecules, oxidative and nitrosative stress, and also on the growth factors and matrix metalloproteinases.

P3271

Upregulated expression of interleukin-33 and alternative activation of macrophages in a model of an acute exacerbation of asthma

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The role of alveolar macrophages (AM) in the pathogenesis of an acute exacerbation of asthma is poorly understood. In a clinically relevant mouse model, we have shown that AM are activated to secrete pro-inflammatory cytokines, and that this activated macrophages and the mechanism of activation. Female BALB/c mice were systemically sensitised to ovalbumin (OVA) and received chronic low-level challenge with aerosolised OVA for 4 weeks. Following this, mice received a single moderate-level challenge to induce airway inflammation simulating an acute exacerbation. AM and tissues were collected 4 hours later. Control groups included naive animals, and mice that only received either chronic challenge or a single moderate-level challenge. AM from an acute exacerbation exhibited significant expression of pro-inflammatory cytokines, including mRNA for arginase-1, PIZZI, Ym1 and etoxacin-2. These AM also exhibited elevated expression of cell surface proteins associated with antigen presentation to T cells, including CD86 and MHC class II. In parallel, expression of mRNA for IL-33 in the airway wall was strikingly increased, with evidence of enhanced immunoreactivity for IL-33 in the cytoplasm of airway epithelial cells and plasma cells within the airway wall. Collectively, these data imply an important role for alternatively activated AM in the pathogenesis of an acute exacerbation of asthma and suggest that IL-33 may contribute to the activation of these cells.

P3272

Naturally occurring CD4+ CD25+ FoxP3+ Treg cells are related to the absence of antigen induced airway obstruction in a guinea pig asthma model

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Some allergic asthma individuals did not display airway obstruction after an anaphylactic challenge (dAOAC); however, the mechanism involved in this process is unknown, it has been suggested that regulatory T cells (Tregs) may be involved. We developed a model of airway obstruction-induced by antigenic challenge in guinea pig (GP) to elucidate the potential role of Tregs. In our model, the sensitized GP are intermittently challenged with the antigen (ovalbumin, OA; applied every 10 days). We found two groups of GP ones that showed dAOAC and ones that did not. Then, we evaluated the antigen-induced airway obstruction and hyper-responsiveness (HR) to histamine and identified the population of Tregs in the airway wall. The aim of this study was to examine whether BM-derived dAOAC mice were recipients of the airway wall. Some allergic asthma individuals did not display airway obstruction after an anaphylactic challenge (dAOAC); however, the mechanism involved in this process is unknown, it has been suggested that regulatory T cells (Tregs) may be involved. We developed a model of airway obstruction-induced by antigenic challenge in guinea pig (GP) to elucidate the potential role of Tregs. In our model, the sensitized GP are intermittently challenged with the antigen (ovalbumin, OA; applied every 10 days). We found two groups of GP ones that showed dAOAC and ones that did not. Then, we evaluated the antigen-induced airway obstruction and hyper-responsiveness (HR) to histamine and identified the population of Tregs in the airway wall.

Conclusions: In our model of asthma, the Tregs play an important role in suppressing airway hyper-responsiveness, and that probably Tregs that produce TGF-beta are involved in the attenuation of the HR in this asthma model.

P3273

Overproduction of IL-18 in the lungs induces IL-13 and IFN-γ producing CD4+ T cell in the lungs, and results in airway hyperresponsiveness in Balb/c mice

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We newly established Balb/c background IL-18 transgenic (TG) mice using the human surfactant protein C promoter to drive expression of mature mouse IL-18 cDNA in the lungs. After sensitization on days 0 and 5 with ovalbumin (OVA), mice were challenged (OA) on day 19. Pulmonary inflammations and airway hyperresponsiveness (AHR) were examined on day 20. We previously reported that constitutive mouse mature IL-18 overexpression in the lungs of C57BL/6 mice induces emphysema (Am J Respir Crit Care Med 2007, 176:49-62). In contrast to C57BL/6 IL-18 TG mouse, emphysematous changes were not observed in the lungs of Balb/c IL-18 TG mice. AHR to inhaled acetylcholine were not induced in non-treated Balb/c IL-18 TG mice. However, AHR and airway inflammation were significantly increased in OVA-challenged Balb/c TG mice compared with OVA-sensitized Balb/c IL-18 TG mice. The number of IFN-γ and IL-13 in the bronchoalveolar lavage fluid of IL-18 TG/IL-13 KO mice. This study suggested that overproducing IL-18 proteins in the lungs of Balb/c mice induce IL-13 and CD4+ T cells which may involve in the pathogenesis of asthma.

P3274

The role of bone-marrow derived adult stem cells in asthmatic airway remodeling

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Background and objective: Asthmatic airway remodeling is an abnormal injury/repair process of small airway on the basis of chronic inflammation, in which the quantities of multiple lung parenchyma cells dramatically increase. However, the origin of this process of maladaptive remodeling is still not clearly elucidated. The aim of the study is to examine whether BM-derived adult stem cells are responsible for the massive proliferative cells in asthmatic airway remodeling. Metodos: Adult mice were durably engrafted with BM isolated from GFP transgenic mice. Using GFP BM-chimera mice, OVA-induced chronic asthma model were established. The distribution of BM-derived GFP+ cells in the lung of chronic asthma mice was detected by fluorescence microscopy. The phenotype of BM-derived GFP+ cells in the lungs was analyzed by flow cytometry.

Results: BM-chimera mice were successfully constructed, with no detectable ra-
366. Inflammation and genes in childhood asthma

P3277
Do exhaled non-inflammatory markers correlate with respiratory symptoms and lung function in a longitudinal study of childhood asthma?
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Background: Worldwide the level of asthma control is far from optimal. Asthma management is currently based on symptoms and lung function indices. Non-invasive inflammatory markers like exhaled nitric oxide may have additional value for asthma management. Little longitudinal data are available.

Aim: To study the relationship between non-invasive inflammatory markers and conventional parameters, during stable periods and during exacerbations.

Methods: 40 Children with asthma (aged 5-16yrs), visited the outpatient clinic every two months during one year. In addition, 4 extra visits were planned during an exacerbation. Every visit the asthma control questionnaire (ACQ) was assessed, lung function was performed and non-invasive inflammatory markers (FeNO, and nitrate, 8-isoprostane, interleukin-5 and tumor necrosis factor-alpha in exhaled breath condensate) were measured.

Results: 16 Of the 40 children experienced an asthma exacerbation. No significant correlations were found between non-invasive inflammatory markers and conventional parameters ( Spearman, p > 0.05).

Correlations between conventional parameters and non-invasive inflammatory markers in childhood asthma.

Stable asthma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>0.10 ± 0.07</td>
</tr>
<tr>
<td>NO-FeV1</td>
<td>0.11 ± 0.07</td>
</tr>
<tr>
<td>8-isoprostane</td>
<td>0.02 ± 0.08</td>
</tr>
<tr>
<td>8-isoprostane-ACQ</td>
<td>0.03 ± 0.07</td>
</tr>
<tr>
<td>Nitrate-FeV1</td>
<td>0.05 ± 0.07</td>
</tr>
<tr>
<td>Nitrate-ACQ</td>
<td>0.04 ± 0.06</td>
</tr>
<tr>
<td>IL-5-FeV1</td>
<td>0.15 ± 0.10</td>
</tr>
<tr>
<td>IL-5-ACQ</td>
<td>0.10 ± 0.07</td>
</tr>
<tr>
<td>TNFα-FeV1</td>
<td>0.10 ± 0.59</td>
</tr>
<tr>
<td>TNFα-ACQ</td>
<td>-0.08 ± 0.11</td>
</tr>
</tbody>
</table>

Data were expressed as mean ± standard error.

Conclusions: This study showed that exhaled non-inflammatory markers provide additional information about childhood asthma compared to conventional parameters.

P3276
Analysis of P2Y12 receptor responsiveness to cystein leukotrienes
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Leukotriene E4 (LTE4), the most stable of the cysteine leukotrienes (cysLT), binds poorly to classical type 1 and 2 cysLT receptors although it may potentially induce bronchial constriction, airway hyperresponsiveness and inflammatory cell influx to the lungs of asthmatic individuals. Evidence of the presence of a previously unidentified LTE4 receptor has also been provided in CysLT1/CysLT2 double knock out mice. A recent study has suggested that purinergic receptor P2Y12 is required for LTE4 mediated pulmonary inflammation in a mouse model of asthma.

The aim of the study was to characterise the responsiveness of human P2Y12 to cystein leukotrienes. A model of human CysLT1, CysLT2 and P2Y12, transiently overexpressed in HEK293 cells was used and responsiveness to different agonists was measured using intracellular calcium and cAMP assays. The responsiveness of human P2Y12 stably overexpressed in CHO cells was also analysed using a β-arrestin recruitment assay. CysLTs induced concentration dependent calcium mobilisation in cells overexpressing CysLT1 and CysLT2 but failed to induce any calcium response in cells expressing P2Y12 or P2Y2+R2+G16. In contrast, a selective P2Y12 agonist 2-MeSADP, induced specific calcium flux in cell expressing P2Y12+G16. Similarly, specific response to 2-MeSADP, but not to cysLTs was also observed in cells expressing P2Y12 when intracellular cAMP and β-arrestin signalling was analysed. These results suggest that LTE4, as well as other cysLTs may not activate intracellular signalling acting through human P2Y12 and another LTE4 specific receptor has yet to be identified.
Comparison of online single-breath versus multiple-breath exhaled nitric oxide at school entry in a cohort of unselected children

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Despite requiring less cooperation there are no standards for online multiple-breath (mb) measurements of exhaled nitric oxide (eNO) with uncontrolled flow rate and no studies comparing them to more difficult online single-breath (sb) eNO measurements in young children.

Online eNOmb and eNOsb were measured by a chemoluminescence analyzer connected to an ultrasonic flowmeter in N=73 children of a birth cohort of unselected children at a mean±SD age of 6.1±0.62 years. During measurements, we aimed for 20 tidal breathing manoeuvres for eNOmb and for 3 eNOsb manoeuvres according to current standards. We compared both techniques by standard comparison methods including regression analysis and Bland-Altman plots.

After strict screening, control, eNOmb and eNOsb measurements were acceptable in n=56 and n=53 children, respectively. Paired data were available for n=46 children methods including regression analysis and Bland-Altman plots.

Introduction: Exhaled nitric oxide (FeNO) may be a biomarker for asthma but clinical trials where FeNO is used to guide asthma treatment have been disappointing. Exhaled NO measurements may not be suited to individuals with increased variability of values. We hypothesised that the variability of FeNO measurements is heterogeneous within a population and sought to describe factors associated with increased variability for repeated measurements of FeNO.

Methods: Children with and without asthma were recruited from the community and completed respiratory questionnaires and underwent an initial phenotyping assessment which included spirometry, bronchodilator response and skin prick reactivity. Exhaled NO was measured every two months over a 12 month period. The coefficient of variation (CV) for FeNO measurements was calculated for each individual.

Results: One hundred and eighty children were recruited including 49 with asthma and 89 FeNO measurements were made (median 5 measurements per child). Eighty two children and 252 FENO measurements were available. The following were not associated with altered CV: asthma, eczema or hayfever; male gender; body mass index; skin prick reactivity; spirometry; bronchodilator response; exposure to pets, smokers or damp at home. There was an inverse relationship between age and FeNO CV (rho= -0.12, p=0.258, n=93). Among the asthmatic children, there was no correlation between FeNO CV and treatment step or dose of inhaled steroid.

Conclusions: Measurements of FeNO CV are variable between individuals. Younger age, but not atopy, asthma status or treatment, is associated with increased variability in FeNO over 12 months.
P3284
Abnormalities in spirometry, impulse oscillometry and exhaled nitric oxide in the university freshmen who have outgrown of bronchial asthma
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Background: Incidence of asthma, particularly in childhood, is rising. Current asthma prevalence is higher in children than in adults, suggesting that children with asthma may outgrow their disease. It has been long believed that the prognosis for asthma occurring in infancy or childhood is good, and that in most patients the symptoms would resolve by the age of puberty. However, little is known about the lung function of outgrown subject. In this study, we recruited the subjects who had outgrown of asthma and performed spirometry, impulse oscillometry and exhaled nitric oxide (eNO) measurement.

Methods: The freshmen in our university with a history of asthma (group A, n=54) and without a history of asthma (group B, n=63) were recruited. All group A subjects (n=33) reported no symptoms and underwent no treatment. Lung function was estimated by CHEST-HIO1001 (CHEST, JAPAN). Impulse oscillometry was performed using MostGraph (CHEST, JAPAN). Exhaled NO level was measured by NO analyzer (NIEVERS NOA, USA).

Results: FEV1% was significantly lower in group A than in group B (88.8±6.1% vs 91.2±4.6%; p=0.01). The mean levels of 8%FEV1 and Vdot50 and Vdot25 were lower in group A than in group B, though not significant. The levels of RS-20 and Res were significantly higher in group A than in group B (RS-20: 0.81±0.07 cmH2O/L/s vs 0.62±0.05 cmH2O/L/s; p=0.03) (Fres: 7.9±0.6 vs 6.4±0.3 Hz; p<0.01). Also, the level of eNO was significantly higher in group A than in group B (47.9±22.4 ppb vs 37.4±22.6 ppb; p<0.01).

Conclusions: The subjects who had outgrown of asthma still have impaired lung function, a follow-up examination of lung function may be needed.

P3285
8-isoprostane in exhaled breath condensate in healthy and asthmatic children in relationship with tobacco smoke exposure
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Introduction: 8-isoprostane is an oxidative stress marker, which rises in asthma and in exposure to tobacco smoke.

Objectives: 1) Differences in the concentration of 8-isoprostane in exhaled breath condensate (EBC) between asthmatics and healthy children. And also between children with recurrent wheezes and healthy preschool children. 2) Relationship between levels of 8-isoprostane and passive smoke exposure.

Methods: 70 children (6 to 14 years) were recruited in 2 groups: 40 asthmatic and 30 healthy children. Also 46 children (8 months to 5 years) were recruited in other 2 groups: 25 with recurrent wheezes and 25 as controls. EBC was collected through one-way valve bag. Data about number of smokers living with the child, cigarettes/day and the smoking place was asked.

Results: 8-isoprostane concentrations were lower between in the group of healthy children than in children with asthma (p<0.004, Mann-Whitney U: 343, mean difference: 6.2 (4.7)). Moreover 8-isoprostane levels differ according to smoking habits of parents (ANOVA F=28.8, P<0.001) and children whose parents smoke at home have higher levels than those of nonsmoking parents (mean difference 22.4, p=0.003). Similarly happened to children from 8 months to 5 years (ANOVA F=23, p<0.001) and (mean difference 141.3, p<0.001).

Conclusions: There are significant differences in the concentrations of 8-isoprostane in EBC from asthmatic children 6-14 years old and healthy and also in preschool children. 2. Passive exposure to tobacco smoke increases concentrations of 8-isoprostane, in the EBC of children in both age groups.

Method: FeNO was measured during sedation in 253 healthy symptom-free 1-month-old neonates in relation to infant spirometry testing. The children belong to the COPSAC clinical birth cohort born to asthmatic mothers. The risk factor analyses included genetic variants in DENND1B, Filaggrin and ORM1,3, anthropometric; demographics; socioeconomic status; paternal atopic history; maternal intake of paracetamol, antibiotics, smoking during third trimester of pregnancy; and pathogenic bacterial colonization of the neonatal airway.

Multivariate analyses were done using generalized linear models.

Results: Median neonatal FeNO level was 16.0 ppb (Q1-Q3, 12.0-22.0 ppb). The multivariate effect of DENND1B risk allele, rs2786098, (major allele) was significantly associated with increased levels of FeNO (additive model, β-coefficient, 2.909 ppb, 95% CI, 0.38-5.43; P=0.02). Children with atopic fathers also showed increased values of FeNO (β-coefficient, 2.909 ppb, 95% CI, 0.38-5.43; P=0.02).

None of the remaining genetic or environmental risk factors were associated with neonatal FeNO levels.

Conclusion: Variants in the DENND1B locus of chromosome 1q31.3 and paternal atopy are associated with elevated FeNO levels in 1-month-old newborns prior to development of any atopic symptoms. These findings suggest that the DENND1B risk allele confer an increased risk of wheezy illnesses through modifications associated with NO metabolism very early in life.

P3287
Interleukin-10 polymorphisms influence the neonatal immune response and may be a risk factor for childhood allergic disease and wheeze
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Background: The interleukin-10 gene (IL10) encodes the anti-inflammation cytokine IL-10, which is crucial for the development of immune tolerance and T cell regulation. IL-10 polymorphisms were proposed to influence the asthma phenotype including pulmonary function. We studied the influence of IL-10 single nucleotide polymorphisms (SNPs) early in life on Th2/Th1 lineage late, T regulatory cell function and pro-inflammatory cytokines. Furthermore, the effect of the SNPs on allergic diseases and wheeze was examined at 3 years of age.

Methods: Cord blood of 200 healthy neonates was genotyped for 8 SNPs and one deletion in IL-10. CBMCs were cultured unstimulated or follow stimulation [Lipid A, peptidoglycan, phytohemagglutinin, house dust mite (Derp1), Derp1+Lipid A]. Treg-marker mRNA expression (FOXP3, GITR, LAG3), Th1/Th2 cytokines, TNF-a and GM-CSF were assessed. A follow-up regarding allergic diseases and wheeze was performed (3ys).

Results: The majority of IL-10 SNPs carriers showed a similar pattern of cytokine secretion and Treg-marker expression with increased IFN-γ and decreased IL-10. The SNPs had different effects in different cytokine secretion and Treg-marker expression after innate and allergic stimulation. Carriers of five IL-10 SNPs and one IL-10 deletion showed increased risk for wheezing or atopic symptoms.

Conclusions: Polymorphisms in IL-10 influence primarily Th1/Th2 cytokine secretion and Treg-marker expression after innate and allergic stimulation early in life. This may be relevant for immune maturation and potentially for childhood atopy and wheeze.

P3288
Phenotyping atopic dermatitis in children by filaggrin status. The COPSAC longitudinal birth cohort study
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Background: Filaggrin null mutations result in an impaired skin barrier function and are associated with atopic dermatitis. Clinical observations suggest a distinct phenotype for patients with the filaggrin null genotype.

Objective: To characterize and compare the clinical presentation and course of atopic dermatitis within the first 7 years of life in children with and without filaggrin null mutations.

Method: The COPSAC cohort is a prospective, longitudinal, birth cohort study of 397 Caucasian children born to mothers with a history of asthma, followed for 7 years with scheduled visits every 6 months as well as visits for acute exacerbations of dermatitis. Atopic dermatitis was defined in accordance with international guidelines and dermatitis reactions were accurately described at each visit using 15 predefined localizations and 10 different characteristics.

Results: A total of 170 (43%) of 397 children suffered from atopic dermatitis before age 7. The R501X and 228del4 filaggrin null mutations were associated with a higher number of acute visits (3.6 vs. 2.7; p=0.04), more severe dermatitis (moderate-severe SCORAD 44% vs. 31%; p=0.14), more widespread dermatitis (10% vs. 6% of the body, p<0.001), an earlier age at onset of dermatitis (246 vs. 473 days, p<0.001), dermatitis more often localized at exposed areas (hands, feet, extensor areas, cheeks), and with dermatitis spots characterized by an up regulation in both acute and chronic markers.
The involvement of genetic and environmental factors in asthma is evident. As miRNAs can both respond to the environment and regulate complex signaling networks at the posttranscriptional level they may be implicated in the disease. In previous studies we have identified dysregulated pulmonary miRNAs in experimental asthma (ERS Barcelona 2010, abstract 6106). In the present study we were interested to see if selected lung miRNAs are also altered in murine peripheral blood and whether these changes are similar in peripheral blood of asthmatic children. MiRNAs were quantified by rt-PCR in blood from ovalbumin sensitized and challenged Balb/c mice and controls. Ten year old children were selected based on the following criteria: current allergic asthma, absence of acute infections and ETS exposure. Age matched controls from the same cohort were included when they never had asthma and were free from acute infections. MiRNAs were quantified in bio-banked blood samples. Out of 10 children with diagnosed asthma 6 had a record of atopic eczema at any time and 4 had had allergic rhinitis ever. A set of 5 differentially regulated miRNAs (miRNA 17-5p, 21, 141, 181a, 451) in murine lung were chosen to be examined in blood samples. MiRNA and paediatric blood samples showed the same trend of regulation compared to healthy controls. In this study we found opposite expression of selected miRNAs in lung tissue compared to blood of mice with an asthmatic phenotype. This expression pattern was similar in human blood with mice of asthmatic children. These results call for further studies to explore blood miRNAs as potential biomarkers in asthma.

P3291
Disregulated peripheral blood miRNAs in murine experimental and human childhood asthma

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Background: Wheeze affects 20-40% of preschool children. Of all wheezers 30% will have persisting symptoms after the age of six that develop into asthma which is characterized by chronic airway inflammation. Whether airway inflammation is a characteristic of preschool wheezing is poorly documented.

Aim: To assess cross-sectional differences in gene expression of several important inflammatory markers in venous blood cells in preschool children with recurrent wheeze compared to healthy controls.

Methods: In total, 202 children with recurrent wheeze (ISAC questionnaire ≥2 wheezing episodes) and 50 children without respiratory symptoms, age 2-3 year were selected. Total RNA was extracted from peripheral blood mononuclear cells. Gene expression of 21 genes was assessed and corrected for geometric mean of the other genes showed a significant relationship between gene expression level and recurrent wheeze. Logistic regression analysis was subsequently conducted.

Results: Gene expression was successfully analysed in 223 children. Expression of the cytokine receptor CAT exhibited highly significant inverse association with recurrent wheeze (ORadjusted 0.65 (0.48-0.88) p=0.005). Expression of interleukin-17 (IL17) showed a statistically significant positive association with recurrent wheeze (ORadjusted 3.04 (1.33-6.92) p=0.008). None of the other genes showed a characteristic of preschool wheezing is poorly documented.

Discussion: A decrease of CAT expression and an increase of IL17 expression was observed in preschool children with recurrent wheeze. This may point towards the importance of different inflammatory pathways in children with preschool wheezing.

P3290
The chitinase-like protein YKL-40 is elevated in children with severe asthma

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Background: YKL-40 is a protein secreted by macrophages and chondrocytes. Previous studies have demonstrated a role of YKL-40 in asthma. The expression of the chitinase-like protein known to be a chitinase and a serine protease. YKL-40 in relation to asthma is not well documented.

Methods: YKL-40 levels were assessed in children with history of asthma, previous wheeze and non-asthmatic control children. The study included 221 children (70 with asthma, 151 controls) of median age 11 years (range 3-17 years). YKL-40 levels were determined using an ELISA assay.

Results: YKL-40 levels were significantly greater in severe asthmatics compared to healthy children, whereas chitotriosidase activity was no different in severe asthmatics compared to healthy children. These results suggest that serum YKL-40 is a genetically influenced, protective biomarker of airway inflammation in children. Taking into account possible effects of the CHI3L1 promoter SNP Rs4950928.

Discussion: YKL-40 levels were significantly greater in severe asthmatics compared to healthy children, whereas chitotriosidase activity was no different in severe asthmatics compared to healthy children. These results suggest that serum YKL-40 is a genetically influenced, protective biomarker of airway inflammation in children. Taking into account possible effects of the CHI3L1 promoter SNP Rs4950928.

Conclusion: Further studies are needed to determine the clinical relevance of the findings and the impact of the associated genetic polymorphism.
optimal TB case management contribute to transmission of TB and development of drug resistance.

Aim: To evaluate the temporal trends of the proportions of treatment success and favourable outcomes in the Member States of the WHO European Region in 2004-2008.

Methods: Aggregated data on definitive treatment outcomes (cured and treatment completed) on a farm are larger in size. We explored the interrelation and independence of these protective effects in the large GABRIELA Surveys.

Results: Farm children have more siblings and less often attend day-care facilities than their rural peers. More siblings and farming conferred independent protection from asthma and allergies. No protection by day-care attendance was found. There was no clear evidence of interaction between family size or day-care attendance and farming. The prevalence of hay fever was 12% among non-farm only children and 2% among farm children with more than 2 siblings.

Conclusion: The inverse association of farming with asthma and allergies is found in all sizes of family, with no clear tendency to total saturation or synergism. This suggests that different mechanisms may underlie these two protective factors. Combinations of family size and farm exposure markedly reduce prevalence of allergic disease and indicate the strength of environmental determinants.

P3294
Polymorphisms in 17q12-21 are associated with asthma exacerbation and lung function in asthmatic children

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Background: More than 15 studies associated genetic variants in 17q21 region with asthma. We aimed to investigate whether amongst Croatian asthmatic children, genetic variants in this region are associated with asthma severity and exacerbation.

Methods: We recruited 423 children aged 6-18 years with physician-diagnosed asthma. Information on hospital admission with asthma exacerbations was retrieved from medical records. Data on wheeze frequency and environmental tobacco smoke (ETS) exposure was collected using validated questionnaire. Lung function (FEV1) was measured using spirometry. We analyzed 35 haplotype-tagging SNPs in 17q21.

Results: We found significant associations between 4 SNPs and hospital admissions (rs12150079, rs7212938, rs2290400, rs8067378). For example, G allele homozygotes in rs12150079 were at higher risk of being admitted to hospital than carriers of A allele (OR 1.85, 95%CI 1.26-2.72, p=0.002); this SNP was also associated with current wheezing. Six SNPs were associated with lung function (rs9635726, rs921651, rs9900538, rs3169572, rs4795403, rs471692). In addition, we observed significant interaction between 3 SNPs (rs12603332, rs8067378, rs9302377) and in vitro ETS exposure in relation to lung function (p<0.04, in the largest children of mothers who smoked during pregnancy; major allele homozygotes had lower FEV1;5 predicted than minor allele carriers, but amongst non-exposed children there was no difference in lung function between different genotype groups.

Conclusion: Variants in 17q12-21 region may be associated with asthma severity and may interact with in vitro ETS exposure in determining lung function amongst asthmatic children.

367. Risk factors and treatment outcomes in multidrug- and extensively drug-resistant tuberculosis

P3295
Temporal trend of treatment in TB treatment outcomes in the WHO European region

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Background: There is scientific evidence that poor treatment outcomes and suboptimal TB case management contribute to transmission of TB and development of drug resistance.

Aim: To evaluate the temporal trends of the proportions of treatment success and favourable outcomes in the Member States of the WHO European Region in 2004-2008.

Methods: Aggregated data on definitive treatment outcomes (cured and treatment completed) on a farm are larger in size. We explored the interrelation and independence of these protective effects in the large GABRIELA Surveys.

Results: During the period 2004-2008, the proportions of treatment success among new TB cases ranged from 64.6% (2.8634/2443) to 76.3% (5.9977/860) and from 61.2% (70,211/114,721) to 72.0% (55,196/76,681) in low (L) vs middle-high (M-H) TB incidence (i.e., TB incidence < 20 vs. ≥ 20 cases per 100,000 population) countries, respectively. Only during the years 2004, 2007 and 2008 the proportion of treatment success was significantly higher in low TB incidence countries (P<0.001). Re-treated cases were successfully treated in low incidence countries during the study period (average treatment success proportion in L and M-H TB incidence countries were 62.3% and 49.7%, respectively; P<0.001). Failure trends were significantly higher in new and re-treated cases in M-H TB incidence countries 9.8% versus 5.0% and 19.6% versus 10.7% respectively; P<0.001).

Conclusion: This analysis confirms that sub-optimal treatment outcomes in new and re-treated TB cases are frequently recorded in the WHO European Region setting. Introduction and/or strengthening of multidisciplinary interventions to improve treatment outcomes are urgently needed.

P3296
Predictors of treatment outcome in multidrug-resistant tuberculosis

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Multidrug-resistant tuberculosis (MDR-TB) is a challenge to control programs. In these cases, treatment is more complex, more expensive and very often less successful.

The purpose of this study was to analyze the factors that could influence (positively or negatively) the outcome.

To examine this issue we used data from the National Tuberculosis Program in Portugal SVG-TB. For the study, we included all MDR-TB cases reported from January 2000 to December 2008. To identify the predictive factors related to the outcome of treatment we used univariate and multiple logistic regression models with the clinical variables.

During the study period 130 patients with MDR-TB were notified, of these 94 (72.3%) were male and 36 (27.5%) female, mean age 42 years old (range 40-44). Forty-six patients (35.5%) had a previous treatment and 39 (30%) were HIV positive. Treatment success (cured or completed treatment) was observed in 80 (61.5%) patients. Susceptibility and use of pyrazinamide or ethambutol, susceptibility and use of a fluoroquinolone, the use of five or more drugs in the treatment regimen, sputum culture conversion after 2 months of treatment were predictors of successful outcome of treatment. Treatment supervision (death, default and failure) was observed in 47 (36.1%) patients. Previous treatment, HIV co-infection, presence of cavitation on the chest radiograph, resistance of two or more drugs than just isoniazid and rifampicin and positive cultures after 2 to 3 month of treatment were predictors of poor treatment outcome. Rapid diagnosis of drug resistance and an appropriate therapy for effective treatment are important conditions for the prevention of spread of resistant strains and control of MDR-TB.

P3297
Risk factors for drug-resistant tuberculosis in the north of Portugal

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Although drug resistance is considered the main threat for tuberculosis control, in Portugal very few studies focused on the risk factors. The aim of this study was to identify risk factors for drug resistance in patients with tuberculosis in the North of Portugal.

We performed a retrospective case-control study involving patients with drug-resistant tuberculosis registered in North of Portugal, between March 2009 and
P3298
Treatment of MDR tuberculosis in Switzerland. A case control study
Werner Karrer, Helena Shang, Patrick Brun.
TBC Unit, Luzerner Hoehenklinik Montana, Crans-Montana, VS, Switzerland

Background: MDR tuberculosis can mostly be cured in western countries, but treatment with second-line drugs is difficult, long-lasting, provided with many side effects and expensive.

Methods: The aim of our study was to follow the patients with MDR Tuberculosis, hospitalized at the Luzerner Hoehenklinik Montana (LHM) between 2005 and 2010, and to control their treatment to full recovery. The information in relation to post clinical treatment was gathered through personal contact with the treating physicians and telephone interviews with the patients.

Results: Of 46 patients with tuberculosis hospitalized at the LHM between 2005 and 2010, five patients were assessed having multidrug resistant tuberculosis. Three suffered from pulmonary tuberculosis, one from tuberculous spondylodiscitis, and one from lymph node tuberculosis. One patient was shown after some weeks of treatment in a second evaluation the laboratory findings not to have MDR Tbc.

Drug therapy was performed with second line antituberculous drugs in combination of 4 to 5 drugs like Aminoglycosides, Ethionamide, Oxazolidinones and Quinolones. Drug therapy was given for at least 12 months. All patients required initially for a prolonged period intravenous drug therapy. In two patients surgery was performed during treatment (resection of the upper lobe of the lung, lymph node resection).

Conclusions: Cases of multidrug resistant tuberculosis are still challenging for physicians and patients as diagnosis may not be evident and treatment remains difficult. In two cases the diagnosis was delayed due to different reasons. Duration of treatment is long and complicated, side effects are frequent and especially the cost of treatment is high.

P3299
Gender and other risk factors for multidrug-resistant (MDR) tuberculosis
(TB) among migrants to Milan, Italy
Alice Rigosio1, Monica Delmaestro3, Maurizio Ferrarise, Giovanni Ferrara3, Nicola Murgia3, Luigi Codecasa1,2,3,1TB Reference Centre- Villa Marelli Institute, Niguarda Hosp, Milan, Italy; 2Respiratory Medicine Inst., University of Perugia and Terni, Terni, Italy; 3Section of Occupational Medicine, Occupational and Environmental Respiratory Diseases and Toxicology, University of Perugia and Terni, Perugia, Italy

MDR-TB is a threat to global TB control. Identification of risk groups is crucial in low prevalence countries for early diagnosis and to limit transmission. retrospective evaluation of TB cases treated at the Villa Marelli Inst., Milan, Italy, in the years 2000-2010. Susceptible TB patients (sTB) and MDR-TB patients were considered for the analysis. Potential risk factors for MDR, such as age, thoracic or extra-thoracic involvement, HIV status, country of origin, etc were evaluated in a logistic regression model.

Results: 91 MDR-TB and 1510 sTB patients were recorded in the study period. HIV seropositive status (OR 3.98, 95% CI: 1.52 -10.39) and being migrant (IM) from Eastern European countries (OR 3.55, 95% CI: 1.33 -9.58) were independently associated to MDR-TB. Stratifying for sex, female subjects from Eastern Europe, South America and Asia had a higher risk than male from the same regions (East-European women OR 10.37 95% CI: 5.25 -22.95; South American women OR 7.06 95% CI: 3.86 -12.94; Asian women OR 4.01 95% CI: 1.63 -9.89). HIV co-infection was present in 13.8% of this group. The intravenous drug use [adjusted odds ratio (OR):3.14, 95% CI:1.33-7.66] and previous treatment (OR: 3.05;95%CI: 1.16-7.98) were found to be risk factors for TB drug-resistance.

In this region, previous tuberculosis treatment and intravenous drug use were risk factors to drug-resistance. HIV co-infection was not a statistical significant risk factor for drug-resistant tuberculosis. Identifying clinical predictors of drug resistance may aid in risk stratification for earlier treatment and infection control.

P3300
Treatment outcomes of MDR-TB patients notified in Romania during 2005-2007
Nicoleta Cioran, Elmina Ibraim, Horia Coco. National TB Program, Marius Nasta Institute of Pulmonology, Bucharest, Romania

Introduction: MDR-TB is a major public health concern for the entire international community, due to the longer duration of transmission of infection and reduced chances to reach a successful treatment outcome in such cases, by comparison with sensitive TB cases.

Aims and objectives: The analysis of treatment outcomes in MDR-TB cases reported in Romania in 2005-2007, by them demographic and clinical characteristics.

Methods: Descriptive retrospective study of treatment outcomes in MDR-TB patients reported in Romania in 2005-2007. Data have been extracted from the database of the National TB Programme - Central Unit.

Results: In those 3 years 2234 MDR-TB cases have been reported, 79.7% males, 50.7% living in urban areas, most of them in 45-54 years age group. Only for 100 patients was notified the association with alcoholism, 15 were prisoners and 13 had HIV co-infection. As diagnosis 51.5% had cavitary and 24.8% extensive cavitary forms of TB. In 2121 MDR-TB cases evaluated, overall success rate was 28.8% (31.4% in 2005, 31.8% in 2006 and 23.2% in 2007 – not final). The highest rate of failure was recorded in 2005 (32.0%). Death rates had a share of over 28% for 2005 and 2006, and 20% for 2007. Highest default rate was recorded in 2007 - 19.1%. For 40 patients reported in 2007 the treatment was still continuing at the time of study and in the group of 2005, 12.6% of outcomes remained unknown.

Conclusions: The success rate overall MDR-TB patients was 28.8% in Romania in 2005-2007. Increased efforts are necessary for earlier detection of such cases and for better management.
In this study we aimed to determine the factors associated with treatment outcome in HIV negative patients with multidrug resistant tuberculosis (MDR TB). The study comprised 64 (43 female and 21 male) patients in whom second line TB treatments were administered in directly observed treatment (DOT) programme. Treatment outcome was determined in 73.4% of the patients. The mean duration time of the treatment was 16.4±8.2 months. Treatment failure was defined as cure in 34 (53.1%), defaulter in 18 (28.1%), successful treatment in 1 (1.6%) and exitus in 3 (4.7%) patients. Also, in 8 (12.5%) patients treatment was incomplete and continued. Adverse effects of the drugs were seen in 39 (60.9%) patients with the frequency of gastrointestinal disturbance (51.5%), psychiatric disorders (15.6%), dermatological effects (12.5%). In logistic regression analysis only presence of cavity and the extensive disease were found to be associated with bacteriologic response, MDR TB is a treatable disease if regular and appropriate treatment is administered.

**P3306**
Treatment outcome of multi-drug resistant tuberculosis treated as outpatient in a tertiary care center
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Introduction: Community-based out-patient treatment for multidrug-resistant tuberculosis (MDR TB) is relatively new concept with reported successful outcomes. The aim of this study is to assess the treatment outcomes of HIV negative MDR TB patients treated as outpatient at a teaching medical care center in Karachi, Pakistan.

Methods: Observational study of culture proven HIV negative MDR TB pa-tients treated at Aga Khan University Hospital, Karachi. Data were collected on predesigned performa regarding patient’s demography, clinical features, drug sensitivity, treatment and outcome.

Results: A total of 53 HIV negative patients (27 males), with mean age of 37±15 years (range 15-76 years), received treatment as outpatient for culture proven MDR TB. 51 patients (96.2%) had pulmonary while 3 patients (5.6%) had extra-pulmonary TB. History of exposure to tuberculosis patients was found in 36 (67.9%) patients. Treatment regimen with 2nd line drugs was decided on individual basis according to DST on sputum culture results. The mean duration of treatment was 18 months. Successful outcome was seen in 25 patients (47.2%), 25 patients (47.2%) were loss to follow up and defaulted while 3 (5.6%) patients remained smear positive at the end of treatment. Success rate was 89.2% in those who completed the treatment.

Conclusion: Community-based out-patient treatment strategy is both feasible and safe for the treatment of MDR-TB patients in resource limited country like Pakistan and this strategy should be integrated into the routine approach to treatment of MDR-TB patients in the country where the expertise are available. High default rate is this strategy is the main challenge which should be addressed.

**P3307**
Treatment outcome of multi drug resistant tuberculosis patients in modified DOTS-PLUS: A new strategy
Rajendra Prasad1, Abhijeet Singh 1, Rajiv Garg1, Irfan Muhammad, Zeeshan Waheed, Javaid A. Khan
Pulmonary Section, Department of Medicine, Aga Khan University, Karachi, Pakistan

Background: The traditional DOTS (Directly Observed Treatment, Short course) strategy is a success in most of the countries but it suffers from high default and loss to follow up rates. Later on, DOTS-PLUS strategy was introduced by WHO which included monthly home visits along with radiological and bacteriological follow up.

Aims and Objective: To study the treatment outcome with second line drugs in patients of MDR-TB in modified DOTS-PLUS strategy.

Methods: A prospective cohort study analysing 98 consecutive patients with MDR-TB attending the Dept of Pulmonary Medicine, CSMUH, between June 2009 to Feb 2010 with follow-up till Feb 2011. All the patients were given medications free of cost as per DOTS PLUS Protocol of India.Treatment included monthly followup,adherence check up, radiological and bacteriological assessment (sputum smear-monthly till conversion then quarterly;culture for MTB-0, 4.6, 18, 24 months), health education and monitoring of adverse effects.

Results: All the patients had resistance to at least isoniazid and Rifampicin with mean no. of 3.02 drugs and were sorerenegative for HIV. Default rate at the end of 6 months and 12 months were observed in 2.1% and 4.1% patients respectively. 5 patients expired in initial 6 months and 2 in next 6 months. Sputum smear and culture conversion at the end of 6 months and 12 months were 80/90 (88.9%) and 75/90 (83.3%) and 81/87 (93.1) and 78/87 (89.7%) respectively. Mean smear and culture conversion time were 3.6±2.1 months and 4.1±2.6 months respectively. Significant side effects were experienced in 14.3% patients.

Conclusions: Culture conversion rates at the end of 6 months and 12 months were 83.3% and 89.7% respectively. Modified DOTS-PLUS strategy can be model for treatment of MDR-TB in private sector.
Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampin, is a growing global concern. Even after successful treatment of TB, there is still the issue of recurrence, of which the rate has been reported to be up to 3.4% in drug susceptible TB. The rate of recurrence could be higher in patients with drug-resistant TB, but comprehensive data is limited. We aimed to elucidate the rate of recurrence among patients with MDR-TB who finished their treatment successfully. A retrospective study was conducted of patients with multidrug-resistant tuberculosis (MDR-TB) to elucidate the rate of recurrence after successful treatment. Of 123 MDR-TB patients, 90 were declared as “cured” or “treatment completed” after individualized therapy. Among 75 successfully treated MDR-TB patients with at least 1 complete year of follow-up, 4 (5.3%) had recurrence.

**Baseline characteristics of 4 patients with recurred MDR-TB**

<table>
<thead>
<tr>
<th>Sex / Age</th>
<th>Treatment duration (months)</th>
<th>Resistance profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 M / 32</td>
<td>First treatment: 34</td>
<td>INH, RIF, SM, EMB, PAS, OFLX, PZA</td>
</tr>
<tr>
<td>#2 M / 49</td>
<td>Second treatment: 30</td>
<td>INH, RIF, SM, EMB, PAS, OFLX, PZA</td>
</tr>
<tr>
<td>#3 F / 33</td>
<td></td>
<td>INH, RIF, SM, EMB, PAS, OFLX, PZA</td>
</tr>
<tr>
<td>#4 F / 31</td>
<td></td>
<td>INH, RIF, SM, EMB, PAS, OFLX, PZA</td>
</tr>
</tbody>
</table>

All patients with recurred MDR-TB were documented as “treatment completed” after recurrence. Treatment of MDR-TB is possible after recurrence of MDR-TB, especially in the “treatment completed” group.

**P3308 Recurrence after successful treatment among patients with multidrug-resistant tuberculosis**

Chul-Gyu Yoo¹, Jinwoo Lee¹, Young Sik Park¹, Sang-Min Lee², Jae-Joon Yim², Seok-Chul Yang¹, Young Whan Kim¹, Young-Soo Shim¹, Sang Koo Han¹
¹Department of Internal Medicine and Lung Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; ²Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea

**Methods:** We conducted a retrospective study of patients with multidrug-resistant tuberculosis (MDR-TB) to elucidate the rate of recurrence after successful treatment. Of 123 MDR-TB patients, 90 were declared as “cured” or “treatment completed” after individualized therapy. Among 75 successfully treated MDR-TB patients with at least 1 complete year of follow-up, 4 (5.3%) had recurrence.

**Results:**

- **Baseline characteristics:**
  - **Sex / Age:**
    - #1 M / 32, First treatment: 34 months
    - #2 M / 49, Second treatment: 30 months
    - #3 F / 33
    - #4 F / 31
  - **Resistance profile:**
    - INH, RIF, SM, EMB, PAS, OFLX, PZA

**Conclusion:** Treatment of MDR-TB is possible after recurrence of MDR-TB, especially in the “treatment completed” group.
chlorine) or water. 48h after 1, 3, 5 and 7 instillations, we measured airway reactivity to methacholine (Flexivent), cellular inflammation in broncho-alveolar lavage (BAL), lung cytokines, and serum OVA-specific IgE. Later, methacholine reactivity 48h after a single combined nasal NaClO-OVA exposure was assessed in mice pretreated with the neurokinin1 receptor antagonist RP67580, in knock-out mice deficient in the transient receptor potential (TRP) channel A1 (TRPA1−/−) or V1 (TRPV1−/−) and in mast cell deficient mice (Kit−/−Kitw−/−). Results: Combined nasal NaClO-OVA exposure induced airway hyperreactivity (AHR) to methacholine in the absence of airway inflammation and OVA specific IgE. AHR was already induced after a single combined exposure to NaClO-OVA and it was not observed after either OVA or NaClO alone. The AHR response was reduced after pretreatment with RP67580. NaClO-OVA induced AHR in TRPV1−/− mice, but not in TRPA1−/− mice and mast cell deficient deficient.

Conclusion: Combined nasal NaClO-OVA exposure induces AHR in the absence of allergic inflammation. This effect appears to involve TRPA1, mast cells and release of substance P, suggesting a neuro-immune interaction.

P3313

LS142011 Abstract: Changes in the proteome upon dermal sensitization in a mouse model of chemical-induced asthma

Steven Haenen, Elke Cllynen, Vanessa De Vooght, Peter Hoet, Ben Nemery, Jeroen Vanrooibeek. Occupational, Environmental & Insurance Medicine Research Unit of Lung Toxicology, KU Leuven, Leuven, Belgium; BIOMED Research Institute, Hasselt University, Diepenbeek, Belgium

In follow up of our studies on proteomic changes in a validated mouse model of immunologically mediated chemical-induced asthma, using toluen-2,4-disooylane (TDL) as a sensitizer [1] we evaluated the temporal changes at early time points following dermal sensitization. The identification of biomarkers of sensitization could help to move diagnosis to an earlier (pre-clinical) stage. We explored the proteome of the auricular lymph nodes and serum of mice dermally sensitized to TDI.

Mice were treated once (day 1) or twice (day 1 and 8) with TDI or with the vehicle (acetone-olive oil, 2:3, control) on both ears. Auricular lymph nodes and serum were collected three days later. Two-dimensional difference gel electrophoresis was used to analyze the differential proteins (p<0.05) of TDI-sensitized mice (n=12) vs. control mice (n=12). Proteome analyses of the auricular lymph nodes resulted in 39 and 86 differential proteins and of serum in 7 and 16 differential proteins, after 1 and 2 sensitizations, respectively. Identification (MALDI-TOF MS) of these proteins mainly showed structural (e.g. vimentin), immune related (e.g. lymphocyte specific protein-1) and oxidative stress related proteins (e.g. peroxiredoxin 6) in both the lymph nodes and the serum.

Now, a software based pathway analysis of the differential proteins is performed (Anadine Genomics). This will give more insight in the cellular and molecular events involved in early sensitization, leading to chemical-induced asthma. Possible biomarkers among the differential proteins will be validated.

Reference:

P3314

Inhalation of nano-sized titanium dioxide particles aggravates airway inflammation in allergen-challenged mice

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Titanium dioxide (TiO2) nanoparticles are manufactured worldwide and although TiO2 is chemically inert, it may have adverse health effects especially in sensitive populations. The use of nanomaterials has increased over the past years and the detrimental effects on various airway diseases are poorly characterized. Thus we investigated if a single exposure of TiO2 before or during ovalbumin (OVA)-challenge could promote airway inflammation in mice with allergic airway disease.

BALB/c mice were sensitized to OVA (10 μg i.p.) on day 0 and 14, then challenged with nebulized 1% OVA for 30 min on day 29.32 and 34. Lung exposure of aerosolized TiO2 was performed before (day 28) and during OVA challenge (day 33). The approximated deposited dose of TiO2 in the mouse lung was estimated to be 0.53 mglm3 (2h, nose-only exposure). The experiment ended on day 35 with a 48h inhalation of bronchial reactivity to methacholine and inflammatory cell counts in bronchoalveolar lavage (BAL). Total inflammatory cell counts in BAL was increased both when TiO2 was exposed on day 28 and day 33 (both p<0.05) compared to exposure to only OVA. When mice were exposed for TiO2 before OVA challenge there was a larger decline in respiratory compliance (p=0.03) and a greater impact on peripheral airways (tissue resistance and tissue elastance both p<0.05) compared to TiO2 administrated during the OVA-challenge and to animals exposed to only OVA. In conclusion, we aimed to study effects of combined exposure of nanoparticles and pro-allergic proteins in a mouse model of asthma, indicating that TiO2 administration before and during allergen-challenge have proinflammatory effects in peripheral airways.

P3315

Endotoxin exposure protects against new onset of pollen sensitisation

Grethe Elholm1, Glyndir Onstand1, Torben Sigsgaard1, Gert Doekes2, Joannis Basinas3, Charlotte Hjort1, Pernille Milvang Gronager4.

Vivi Schlünssen1, 2. Dept. of Environmental and Occupational Medicine, Aarhus University, Aarhus, Denmark; 3Clinic of Occupational Medicine, Alborg Hospital, Aarhus University Hospital, Alborg, Denmark; 4Division of Environmental Epidemiology, Utrecht University, Institute for Risk Assessment Sciences, Utrecht, Netherlands; 5Dept. of Quality and Research, Regional Hospital of Viborg, Skive, Kjellerup, Viborg, Denmark; 6Research ALK Abelló, ALK Abelló, Hørsholm, Denmark

Background: Farmers are exposed to a wide range of organic and microbial components. We studied the relation between farm-related endotoxin exposure and changes in atopic sensitisation over time in young adults in The Danish Farming Cohort (SUS).

Method: The SUS cohort (n=1166) was examined twice with a 15 year follow-up period. Specific IgE was evaluated against cat, birch, grass, HDM and storage mite allergens were determined (ADVIA Centaur, ALK Abelló). Sensitisation was defined as an IgE≥0.35 KU/L, and atopy was defined as sensitisation to one or more of the 5 allergens tested for. Personal average yearly exposure to endotoxin during the follow-up period was estimated from more than 500 personal inhalable dust measurements and a farm-specific internal job exposure matrix.

Results: New onset atopy was negatively associated with endotoxin exposure in a dose dependent manner (Table 1). Endotoxin exposure was not seen to be related to new onset of mite sensitisation. In contrast, all levels of endotoxin exposure showed a significant and strong protective effect against new onset of pollen sensitisation.

Table 1. Logistic regression analysis on endotoxin and new onset sensitisation

<table>
<thead>
<tr>
<th></th>
<th>Endotoxin</th>
<th>Atey</th>
<th>OR (95% CI)</th>
<th>Pollen</th>
<th>OR (95% CI)</th>
<th>Mites</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. quantile</td>
<td>0.75</td>
<td>0.37-1.54</td>
<td>0.56 (0.18-0.73)</td>
<td>2.28 (0.94-5.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. quantile</td>
<td>0.90</td>
<td>0.70-1.19</td>
<td>0.14 (0.06-0.36)</td>
<td>1.47 (0.37-3.83)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4. quantile</td>
<td>0.89</td>
<td>0.22-0.89</td>
<td>0.21 (0.09-0.47)</td>
<td>1.14 (0.41-3.35)</td>
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</tbody>
</table>

*p<0.05 The model is adjusted for farm childhood, familial atopic disposition, pets and smoking status.

Conclusion: These analyses suggest endotoxin exposure to have a significant protective effect against new onset of pollen sensitisation.

P3316

Reduction of diesel exhaust-induced health effects by using a vehicle cabin air filter

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Exposure to air pollution is associated with adverse health effects. During exposure in traffic, air pollution concentrations may reach levels that cause symptoms and about diseases. One way to counteract such effects can be to use an air filter in order to prevent particles and gases from entering the vehicle cabin. The aim of the present study was to evaluate the efficacy of two filters to reduce diesel exhaust (DE) related health effects.

Material and Methods: 30 allergic and non-allergic subjects were exposed in an exposure chamber on four occasions during 1 hour; to filtered air, unfiltered DE filtered by an ultrafine particle (UFP) filter and a UFP+AC filter. The combination filter (UFP + active charcoal) significantly reduced PM1 by 74% but also NO2 by 75% and hydrocarbons by 50%. Headache, dizziness, eye irritation, nasal irritation, unpleasant smell and throat irritation increased significantly after exposure to unfiltered diesel exhaust compared to filtered air. Symptoms were significantly reduced by the UFP filter with active charcoal (UFP+AC), in random blind order.

Results: The UFP filter reduced PM1 by 46%, while the UFP+AC filter not only reduced PM1 by 74% but also NO2 by 75% and hydrocarbons by 50%. Headache, dizziness, eye irritation, nasal irritation, unpleasant smell and throat irritation increased significantly after exposure to unfiltered diesel exhaust compared to filtered air. Symptoms were significantly reduced by the UFP+AC filter and were also associated with small but significant improvements in lung function (FEV1-, FEF25-75). The UFP filter without charcoal was far less efficient.

Conclusions: The combination filter (UFP + active charcoal) significantly reduced ultrafine particle, NO2 and HC concentrations from diesel exhaust, and significantly improved symptoms and lung function. The study indicates that vehicle cabin air filters should not only contain an ultrafine filter component, as the addition active charcoal was necessary to improve symptoms and respiratory health.
P3317 Osteopontin and soluble mesothelin-related peptide levels in malignant and benign diseases due to environmental asbestos exposure and healthy people with environmental asbestos exposure

Mehezt Bayram1, I. Aliks2, I. Nureise2, I. Ismail Beni3, 1 Chest Disease, Sivas Numune Hospital, Sivas, Turkey; 2 Thoracic Surgery, Sivas Numune Hospital, Sivas, Turkey; 3 Biochemistry, Gaziosmanpasa University Medicine School, Tokat, Turkey.

Objective: To determine osteopontin and soluble mesothelin-related peptide (SMRP) levels in malignant mesothelioma (MM) patients, in subjects with pleural plaques (PP) due to environmental asbestos exposure and in healthy subjects with environmental asbestos exposure.

Methods: Blood samples were taken from 279 residents from villages close to plaques (PP) due to environmental asbestos exposure and in healthy subjects. Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects from villages close to OU, 123 healthy subjects from villages >26 km distant to OU and 24 MM patients.

Results: Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 21.207, 8.953, 9.725 ng/mL respectively. Mean serum SMRP levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 4.59, 1.0, 1.11 and 1.12 ng/mL respectively. Mean levels of both biomarkers were significantly higher in MM patients than in subjects with PP and healthy subjects with environmental asbestos exposure. The two biomarkers have no superiority to each other.

P3318 Adipokine adipin is associated with the degree of parenchymal fibrosis in asbestos-exposed patients

Serap Lisli Karbal, Uzafi Lerahtinski, Riina Niinenniemi, Panu Oksa, Tuula Viirkola, Ritta Jarvenpaa, Jukka Uitti, Tiina Moilanen.

Objective: To investigate the role of adipin in the pathogenesis of asbestos-induced lung disease.

Methods: Blood samples were taken from 279 residents from villages close to plaques (PP) due to environmental asbestos exposure and in healthy subjects. Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 21.207, 8.953, 9.725 ng/mL respectively. Mean serum SMRP levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 4.59, 1.0, 1.11 and 1.12 ng/mL respectively. Mean levels of both biomarkers were significantly higher in MM patients than in subjects with PP and healthy subjects with environmental asbestos exposure. The two biomarkers have no superiority to each other.

P3319 Short-term exposure to concentrated ambient particles increases airway hyperresponsiveness in normal mice

TUESDAY, SEPTEMBER 27TH 2011

To air pollution with increase of hospital admissions for respiratory diseases. This study investigated if short-term exposures (1-hour) to relatively low levels of concentrated ambient fine particles (CAP) induce bronchial hyperresponsiveness and lung inflammation in mice. 45 Balb/C mice divided at two groups: 22 exposed to filtered air (FA) and 23 exposed to CAP (20 μg/gm3) for 24 hours. There was a decrease of PEF at basal, 6.25 and 12.5 mg/mL. Mch (p<0.01) was statistically different for the CAP compared to FA; in relation the dose, there was an increase of Per at basal, PBS (p<0.05) and 50 mg/mL. Mch (p<0.01) in CAP when compared to FA; and was also observed a decrease of F/I at basal (p<0.01), PBS, 6.25 and 12.5 mg/mL. Mch (p<0.05). BALF showed an increase in the total cells number (p<0.01), macrophages (p<0.01) and neutrophils (p<0.05) in the CAP when compared to FA. Our findings show that even though a daily mean concentration of PM2.5 below the average daily level recommended by the World Health Organization (25 μg/gm3), a daily exposure to CAP can be a triggering pulmonary responsiveness and the increase in the lung inflammatory infiltration.

P3320 Intratracheal fiber glass instillation in rats: Bronchoalveolar lavage interleukin8 levels

Bianca Domsokos Hancu, Monica Pop, Mihaela Iliesu. Pulmonology, Clinic Pu

Numune Hospital, Sivas, Turkey; 3Biochemistry, Sivas State Hospital, Sivas, Turkey; 4Chest Disease, Yedikule Teaching Hospital for Chest Diseases and Thoracic Surgery, Istanbul, Turkey; 5Biochemistry, Gaziosmanpasa University Medicine School, Tokat, Turkey.

Objective: To investigate the role of adipin in the pathogenesis of asbestos-induced lung disease.

Methods: Blood samples were taken from 279 residents from villages close to plaques (PP) due to environmental asbestos exposure and in healthy subjects. Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 21.207, 8.953, 9.725 ng/mL respectively. Mean serum SMRP levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 4.59, 1.0, 1.11 and 1.12 ng/mL respectively. Mean levels of both biomarkers were significantly higher in MM patients than in subjects with PP and healthy subjects with environmental asbestos exposure. The two biomarkers have no superiority to each other.

P3317 Osteopontin and soluble mesothelin-related peptide levels in malignant and benign diseases due to environmental asbestos exposure and healthy people with environmental asbestos exposure

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Objective: To determine osteopontin and soluble mesothelin-related peptide (SMRP) levels in malignant mesothelioma (MM) patients, in subjects with pleural plaques (PP) due to environmental asbestos exposure and in healthy subjects with environmental asbestos exposure.

Methods: Blood samples were taken from 279 residents from villages close to plaques (PP) due to environmental asbestos exposure and in healthy subjects. Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects from villages close to OU, 123 healthy subjects from villages >26 km distant to OU and 24 MM patients.

Results: Mean serum osteopontin levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 21.207, 8.953, 9.725 ng/mL respectively. Mean serum SMRP levels for MM, PP, asbestos-exposed healthy subjects and healthy subjects not exposed to asbestos were 4.59, 1.0, 1.11 and 1.12 ng/mL respectively. Mean levels of both biomarkers were significantly higher in MM patients than in subjects with PP and healthy subjects with environmental asbestos exposure. The two biomarkers have no superiority to each other.

P3318 Adipokine adipin is associated with the degree of parenchymal fibrosis in asbestos-exposed patients

Serap Lisli Karbal, Uzafi Lerahtinski, Riina Niinenniemi, Panu Oksa, Tuula Viirkola, Ritta Jarvenpaa, Jukka Uitti, Tiina Moilanen.

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TUESDAY, SEPTEMBER 27TH 2011

Hosein Noham, Karen Yoshizaki1, Alessandra Choqueta Toledo2, Beatriz Manguerra Saravia-Romah-lo3, Adair Aparecida Santos Alleman4, Mariguela Macchine1, Paulo Hilário Nascimento Sadilha1, 1 Department of Pathology, Laboratory of Experimental Air Pollution, School of Medicine, University of Sao Paulo, Sao Paulo, SP, Brazil; 2 Department of Medicine, Laboratory of Experimental Therapeutics, School of Medicine, University of Sao Paulo, Sao Paulo, SP, Brazil.

Epidemiological studies show an association between short periods of exposure to air pollution with increase of hospital admissions for respiratory diseases. This study investigated if short-term exposures (1-hour) to relatively low levels of concentrated ambient fine particles (CAP) induce bronchial hyperresponsiveness and lung inflammation in mice. 45 Balb/C mice divided at two groups: 22 exposed to filtered air (FA) and 23 exposed to CAP (20 μg/gm3) for 24 hours. There was a decrease of PEF at basal, 6.25 and 12.5 mg/mL. Mch (p<0.01) was statistically different for the CAP compared to FA; in relation the dose, there was an increase of Per at basal, PBS (p<0.05) and 50 mg/mL. Mch (p<0.01) in CAP when compared to FA; and was also observed a decrease of F/I at basal (p<0.01), PBS, 6.25 and 12.5 mg/mL. Mch (p<0.05). BALF showed an increase in the total cells number (p<0.01), macrophages (p<0.01) and neutrophils (p<0.05) in the CAP when compared to FA. Our findings show that even though a daily mean concentration of PM2.5 below the average daily level recommended by the World Health Organization (25 μg/gm3), a daily exposure to CAP can be a triggering pulmonary responsiveness and the increase in the lung inflammatory infiltration.

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Conclusion:
All production workers displayed airway inflammation characterized by increased sputum neutrophilia compared to unexposed controls. 8-isoprostane (8-iso) values were measured in officers and controls since August 2009 to March 2010 in Monza, Italy. Active smokers and current smokers 59% [95%CI 52.4-66.0] and non-smokers 56% [95%CI 50.6-62.0]). PM10 exposures are related to increased 8-iso levels in the whole study group. There were no differences in neutrophil levels between smokers and non-smokers.

P3324
Sputum neutrophilia and annual decline of FEV1 in dust exposed workers

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In a previous study in the smelting industry we found a significant relationship between dust exposure and accelerated annual decline in FEV1. The aim of the present study was to investigate the association between annual decline in lung function and different inflammatory markers in induced sputum from the production workers.

Methods: Employees (n=76 (27 current smokers)) who had been part of a longitudinal study (9-13 years) including spirometry (>6 measurements) and respiratory questionnaires, performed induced sputum and exhaled NO.

Results: All workers had neutrophil inflammation compared to unexposed controls. However neutrophel levels in sputum samples did not differ between workers with annual decline in FEV1 (>45ml - upper tertile) compared to workers with annual decline in FEV1 (15-25ml-lower tertile), 59% [95%CI 56.6-66.2] and 59% [95%CI 51.6-66.4] respectively. There were no differences in the neutrophil levels between current smokers 59% [95%CI 52.4-66.0] and non-smokers 56% [95%CI 50.6-60.6]. Exhaled NO levels were decreased in smokers compared to non-smokers (11.8 pg/ml vs 20.5 pg/ml, p<0.01).

Conclusion: All production workers displayed airway inflammation characterized by neutrophilia. Surprisingly, there were no differences in the neutrophil level when comparing workers with rapid decline in lung function with those with slow decline in lung function. As expected smokers had low levels of exhaled NO, but there was no difference in neutrophil levels between smokers and non-smokers. Sputum neutrophilia was not a marker for increased decline in FEV1.
In urban centres, diesel exhaust particles (DEP) are the most toxic pollutant released from automotive engines, affecting pulmonary health. The aim of this study was to investigate the effects of a chronic period of exposure to DEP (three months) in healthy mice (Yoshizaki et al., 2010) studying whether chronic, near-ambient levels of DEP exposure could induce changes in the lung parenchyma structure and in the profile of inflammatory cells. Male Balb/c mice were divided into two groups: 1) nasal instillation of 10 μL of DEP (n=9) (DEP group). Nasal instillations were performed five days a week for three months. Lung parenchyma was evaluated by quantifying the mean air space chord lengths (Lm) by morphometry (point counting). T lymphocytes total (CD3) and macrophages (Mac-2) densities were analyzed by immunohistochemistry. DEP exposure induced increase of CD3 T lymphocytes when compared to control. No statistical difference was found in macrophages densities. The Lm was larger in DEP animals than controls (p=0.018). These findings indicate that chronic, near-ambient levels of DEP exposure can cause alveolar enlargement and T lymphocytes recruitment, providing a biological link between DEP exposure and the emphysema.

**P3328**
Changes in exhaled breath condensate pH following specific inhalation challenge in patients with occupational asthma to persulfate salts

**Xavier Muñoz, Sara Sánchez-Vidaurre, Meritxell Espuga, Maria-Dolores Untoria, Ferran Morell, Maria-Jesús Cruz. Respiratory, Hospital Vall d’Hebron, Barcelona, Spain**

**Introduction:** Exposure to persulfate salts in hairdressing professionals is one of the most common causes of occupational asthma (OA) in our setting. pH measurement in exhaled breath condensate (EBC) has proven to be a useful, noninvasive method for monitoring pulmonary inflammatory. This study investigates possible changes in EBC pH in patients with OA to persulfate salts following specific inhalation challenge (SIC) testing.

**Material and methods:** The study population included 13 patients with OA caused by exposure to persulfates, diagnosed by a positive SIC (Group 1) and 25 patients exposed to persulfates, but with a negative SIC (Group 2). EBC samples were collected before and after SIC was performed. pH was determined in all samples following degasification with helium.

**Result:** The mean (SD) EBC pH values before and after SIC were 7.65 (0.63) and 7.32 (0.85), respectively, in Group 1, and 7.73 (0.68) and 7.38 (0.66) in Group 2. There were no significant differences in the pH values between the 2 groups. However, when a decrease in EBC pH greater than 0.4 units following SIC was established as significant, 6 patients in Group 1 (43%) and only 1 patient in Group 2 (4%) exceeded this value.

**Conclusions:** Persulfate salts can induce an inflammatory response in patients with OA. A larger percentage of SIC-positive patients showed a significant EBC pH decrease following the test. This fact could contribute to improving the diagnostic yield of SBC.

**This study was funded by grants from the Spanish Ministry of Health (FIS PI050100) and SEPAR.**

**P3327**
Chronic exposure of diesel exhaust particles causes alveolar enlargement in mice

**Kelly Yoshizaki1, Jose Mara Brío1, Alessandra Choqueta Toledo2, Moriya Henrique Takachi1, Adriano Alencar1, Sandra Ferrerlizian1, Paulo Hilário Nascimento Saldiva1, Thais Mauad, Mariangela Macchiome1. 1Department of Pathology, Experimental Air Pollution Laboratory, LMB55, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil; 2Therapeutic Experimental, University of Sao Paulo, Sao Paulo, Brazil; 3Biomedical Engineering Laboratory, Escola Politécnica, University of Sao Paulo, Sao Paulo, Brazil**

In healthy mice, diesel exhaust particles (DEP) are the most toxic pollutant released from automotive engines, affecting pulmonary health. The aim of this study was to investigate the effects of a chronic period of exposure to DEP (three months) in healthy mice (Yoshizaki et al., 2010) studying whether chronic, near-ambient levels of DEP exposure could induce changes in the lung parenchyma structure and in the profile of inflammatory cells. Male Balb/c mice were divided into two groups: 1) nasal instillation of 10 μL of saline (n=9) (control group) and 2) nasal instillation of 30 μg/10 μL of DEP (n=9) (DEP group). Nasal instillations were performed five days a week for three months. Lung parenchyma was evaluated by quantifying the mean air space chord lengths (Lm) by morphometry (point counting). T lymphocytes total (CD3) and macrophages (Mac-2) densities were analyzed by immunohistochemistry. DEP exposure induced increase of CD3 T lymphocytes when compared to control. No statistical difference was found in macrophages densities. The Lm was larger in DEP animals than controls (p=0.018). These findings indicate that chronic, near-ambient levels of DEP exposure can cause alveolar enlargement and T lymphocytes recruitment, providing a biological link between DEP exposure and the emphysema.

**369. Experimental pulmonary hypertension**

**P3330**
Effect of interferon z preparations on IP10 and ET-1 release from human pulmonary artery smooth muscle cells

**Rozenn Quarck1, Hervé Durand 2, Ewa Niño2, Marion Delcroix 1. 1IMM1000, Biomedicine and Health, University of Sao Paulo, Sao Paulo, Brazil; 2UMRS937, IM2S, Anna de Faye 5, Montevrain, France**

Pegylated (PEG) interferons (IFN), used to treat hepatitis C, are associated with lung toxicity and pulmonary hypertension. Pegylation increases stability of the IFN moiety and in vivo half-life, but reduces in vivo anti-viral activity. These effects are related to the size/shape/position of the PEG attachment. There are two marketed PEGIFNs preparations for hepatitis C; PEGIFNα2a and PEGIFNα2b, which are conjugated to 40 KDa and 12 KDa moieties respectively. Endothelin-1 (ET-1) and IP10 are associated with lung inflammation and are induced by IFNs. We investigated the effect of IFNs preparations on ET-1 and IP10 release from human pulmonary artery smooth muscle (HPASM) cells. HPASM cells were treated with IFNs (0.33ng/mL to 30ng/mL). For ET-1, TNFα (10ng/mL) was added. IP10 and ET-1 immunoreactivity was measured by ELISA at 24h.

IFNα preparations induced IP10 with PEGIFNα2a being the weakest inducer (Fig. 1A; n=6; *p<0.05 by two way ANOVA). In TNFα treated cells, IFNα2a, IFNα2b and PEGIFNα2b induced ET-1 above baseline release (Fig. 1B; n=8; *p<0.05 by one way ANOVA vs control; *p<0.05 by two way ANOVA).

**Figure 1**

![Image](image-url)

We conclude that IFNs preparations activate HPASM cells and this may contribute to the lung inflammation seen in some patients. PEGIFNα2a has the larger PEG moiety and induced less ET-1/IP10. Our results suggest ET-1/IP10 are important when considering mechanisms of pulmonary toxicity of IFNs.

**P3331**
Could platelet-activating factor acetylhydrolyase (PAF-AH) predict adverse event in pulmonary hypertension?

**Rezenn Quark1, Herve Durand2, Ewa Ninio2, Marion Delcroix2. 1Respiratory Diseases, Katholieke Universiteit Leuven, Leuven, Belgium; 2UMRS937, INSERM, Paris, France**

Chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) are threatened conditions mostly diagnosed at late stages. Inflammation could play a role in the pathogenesis. The need of new biomarkers, non-invasively measurable may help to improve the diagnosis and follow up. PAF-AH, a plasmatic enzyme, is a predictive risk factor for cardiovascular events. In a prospective study, we have investigated a potential role of PAF-AH in...
P3334
caspase inhibition reduces severe pulmonary hypertension in the AdTGF-β1/SU5416 model of angioproliferative pulmonary hypertension and lung fibrosis
Laszlo Farkas1, Daniela Farkas1, Donatas Kraskauskas1, Jack Gauldie2, Martin Kolb3, Norbert Vokel3,1
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Pulmonary hypertension (PH) is associated with increased mortality in patients with idiopathic pulmonary fibrosis (IPF). The interaction between the fibrotic process and the pulmonary vasculature is incompletely understood. The current study aimed to investigate whether broad spectrum caspase inhibition can reduce severe angioproliferative PH in the combined model of AdTGF-β1 lung fibrosis and the VEGF receptor inhibitor SU5416.

Female Sprague Dawley rats received AdTGF-β1 intratracheally at day 0, as well as one dose of SU5416 s.c. or vehicle. Some AdTGF-β1/SU5416 animals received the caspase inhibitor Z-Asp-CH2-DCB or vehicle (DMSO) from day 6-28. At day 28, invasive pulmonary hemodynamics were assessed. The right lung was inflated for protein and RNA isolation, and the left lung was inflated with formalin and processed for histology.

We detected clusters of VWF+ endothelial cells excluding the lumen of small pulmonary arteries in AdTGF-β1/SU5416, together with severe PH in AdTGF-β1/SU5416 rats vs. AdTGF-β1/CMC. At the same time, lung fibrosis was increased, as indicated by elevated mRNA expression of profibrotic and matrix genes. Western blots showed a significant increase in caspase-3 cleavage in AdTGF-β1/SU5416 rats. Treatment with Z-Asp-CH2-DCB reduced right ventricular systolic pressures by 19.4 mmHg in average in AdTGF-β1/SU5416 animals (P=0.05 vs. DMSO).

In conclusion, our results indicate that angioproliferative pulmonary vasculopathy was induced in this new model, together with severe fibrosis, and that increased apoptosis contributes to both increased fibrosis and vascular pathology.

P3335
Effects of type I, II and III interferons on endothelin-1 release by human pulmonary artery smooth muscle cells
Peter M. George1, Rekha Badiger1, Himi Ghashw1, Neil Galloway-Phillips1, Trevor T. Hansel2, Jane A. Mitchell1,1Department of Cardiothoracic Pharmacology, Imperial College, London, United Kingdom; 2Imperial Clinical Respiratory Research Unit (ICRRU), Imperial College, London, United Kingdom

The potent vasconstrictor and mitogen peptide endothelin-1 (ET-1) is a therapeutic target for the treatment of pulmonary hypertension. Work from our group has shown that ET-1 release by human pulmonary artery smooth muscle cells (HPASMCs) is critically regulated by interferons (IFNs) and TNF. We have shown that type I IFNs and IFNγ and type II IFNγ, but not type III IFNλ, all released in high doses to viral infection, induce ET-1. As viral infection and IFN therapy are increasingly associated with lung toxicity, including pulmonary hypertension, we have investigated the nature of any interaction between IFNs for ET-1 release by HPASMCs. Cells from 3 separate donors were stimulated in 96-well plates with IFNs, IFNγ, IFNλ and -λ (all 10ng/mL). Supernatants were collected after 24 hours and ET-1 concentrations measured by sandwich ELISA. In the presence of TNFα (10ng/mL), type I IFNs (+2 and +3) or type II IFNγ, but not type III IFNλ, induced ET-1 release. Additive release of ET-1 was seen with IFNα/γ and IFNλ/γ but not IFNα/λ. IFNs did not release ET-1 under any condition studied. Type I and II IFNs act independently to stimulate ET-1 from HPASMCs, which reflects what is known about their separate receptor pathways.

Figure 1. Data is mean ± SEM. *P<0.05 one-way ANOVA for combination of IFNs vs IFN alone.

Our finding that IFNγ is inactive in these cells may suggest that type III IFN spares the lung vasculature.

P3336
Roles of sex hormones on bone morphogenetic protein signaling in pulmonary artery differed between testosterone and estrogen
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Background: Epidemiologic studies have revealed the female predominance in the morbidity of idiopathic PAH (pulmonary arterial hypertension) in the world, predicting the outcome in PAH and CTEPH. Circulating PAH-AH activity has been measured in consecutive patients diagnosed with PAH (n=152) and CTEPH (n=115), at the time of right heart catheterization and compared to a control group of healthy subjects (n=115).

Circulating PAH-AH activity was lower in CTEPH and PAH patients compared to controls (37, 95% CI: 33-41; 41, 95% CI: 37-47; 54, 95% CI: 50-60 nmol mL-1 min-1, p<0.0001). In PAH, PAH-AH activity is correlated to total cholesterol (p=0.29, p<0.0002) and to LDL-cholesterol (p=0.26, p=0.001). In CTEPH, PAH-AH activity is correlated to pulmonary vascular resistance (PVR; r=0.21, p=0.02) and to LDL-cholesterol (r=0.22, p=0.01). In PAH, clinical worsening is associated with an elevated PAH-AH activity (36, 95% CI: 32-41 vs. 45, 95% CI: 40-51; p=0.04). PAH patients with a mean pulmonary arterial pressure >50 mmHg, and with CRP≥4 mg/L have increased PAH-AH activity (35, 95% CI: 30-41 vs. 47, 95% CI: 43-52; p=0.02, 37, 95% CI: 32-42 vs. 45, 95% CI: 40-51; p=0.02, respectively).

Our results suggest that PAH-AH could be a prognostic factor in pulmonary hypertension.

P3333
Potential contribution of precursor cells to vascular remodeling in the AdTGF-β1 model of lung fibrosis and pulmonary hypertension
Laszlo Farkas1, Daniela Farkas1, Donatas Kraskauskas1, Jack Gauldie2, Martin Kolb3, Norbert Vokel1,1Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, United States; 2Departments of Medicine, Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada

Pulmonary hypertension (PH) is associated with increased mortality in patients with idiopathic pulmonary fibrosis (IPF). The interaction between the fibrotic process and the pulmonary vasculature is incompletely understood. There is evidence in human and experimental pulmonary fibrosis that precursor cells may play a role in fibrogenesis, and that precursor cells may also be important for vascular remodeling in chronic models of pulmonary hypertension (PH). But the contribution of precursor cells to vascular remodeling and PH in pulmonary fibrosis has not been investigated yet.

This study aimed to investigate the potential contribution of precursor cells to vascular remodeling in the AdTGF-β1 model of lung fibrosis and PH. Female Sprague Dawley rats received AdTGF-β1 or AdDL70 and were sacrificed at different time points (7, 14 and 28 days). Immunofluorescence stainings were performed on 3 μm sections of the left lung after formalin fixation. We detected clusters expressing markers of endothelial progenitor cells (CD133+/WF, CD146+/VEGFR-2) in the pulmonary arteries of AdTGF-β1 animals, mainly after 14 days. We also found cells expressing markers of fibrocytes (CXC4Rα/β-SMA, CXC4Rβ/α-4-hydroxylase, S100A4/CD34), around pulmonary arteries of AdTGF-β1 animals. In contrast, we did not find such cells in or around pulmonary arteries in AdDL70 treated animals.

In summary, our data support the concept that precursor cells may contribute to postcapitotic vascular repair and pulmonary artery muscularization in experimental lung fibrosis. The detailed mechanisms of precursor cell attraction and activation are currently under investigation.
suggesting involvement of sex hormones in the pathogenesis of PAH. Recent studies have identified a role of bone morphogenetic protein (BMP) signaling in the pathogenesis of PAH and we reported that BMP signaling in pulmonary arterial endothelial cells (PAEC) was attenuated under hypoxic condition in vitro and in vivo. 

**Purpose:** The aim is to investigate effects of estradiol (E) and testosterone (T) on the BMP signaling in PAEC and analyze their mechanisms. 

**Materials and methods:** PAEC were cultured and incubated with β-estradiol (10^-7 M), testosterone (10^-8 M), or vehicle under 1%O2 (hypoxia) and 21%O2 (normoxia). BMP signaling including Smad1/5/8, phosphorylated (p) Smad1/5/8 and Id1 was examined by western blotting and quantitative RT-PCR. The effects of HIF (hypoxia-inducible factor) -1α expression on the BMP signaling were also examined.

**Results:** Under normoxia, p-Smad1/5/8 protein and Id1 mRNA were augmented 1.6 and 1.5-fold by E, but suppressed 0.3 and 0.4-fold by T. Under hypoxia, conversely, p-Smad1/5/8 protein and Id1 mRNA were suppressed 0.5 and 0.4-fold by E, but augmented 3.2 and 2.4-fold by T. HIF-1α accumulation led to alteration of BMP signaling similar to hypoxia, whereas HIF-1α inhibitor altered the signaling similar to normoxia.

Discussion: Estrogens could change BMP signaling in PAEC depending on oxygen concentration. Our observations provide the new mechanism how sex hormone affects on BMP signaling, and sex hormones may be novel therapeutic targets in the treatment of PAH.

**P3337**

**Pulmonary hypertension in the newborn GTP-cyclohydrolase 1 deficient mouse is unrelated to endothelium-dependent vasorelaxation potential**

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**Background:** Tetrahydrobiopterin (BH4) is an endothelial nitric oxide (NO)-sensitive (eNOS) cofactor. Its absence results in eNOS uncoupling and a shift from NO to reactive oxygen species (ROS) generation. The hph-1 mouse is deficient in GTP-cyclohydrolase 1 (GCH1) production, resulting in lowered BH4 tissue content. We have previously shown that the hph-1 mouse has pulmonary hypertension secondary to eNOS uncoupling, yet whether similar changes are evident in the newborn is presently unknown. Thus, we evaluated 1-3 day old newborn hph-1 pups and compared them to wild-type mice (C57BL/6xCBA).

**Methods and results:** Lung morphometry, BH4 and its oxidized metabolite BH2 content were measured and near-resistance pulmonary arteries were studied. In control and hph-1 mice, the BH4 lung content is inversely proportional with age, but decreased in the mutant animals (P<0.01). Pulmonary hypertension is evident in the newborn hph-1 as an increase in the right ventricle-to-left ventricle+septum ratio, compared with wild-type mice (P<0.05). In response to the thromboxane A2 analogue (U46619), the pulmonary arteries of hph-1 mice generate less force (P<0.05). In response to 50 μM L-arginine, a significant increase in medial thickness of small pulmonary arteries was evident in the newborn hph-1 mice (P<0.01), when compared with controls, but show a similar vasorelaxant response to eNOS-dependent and -independent stimulation. As compared with wild-type, a significant increase in medial thickness of small pulmonary arteries is evident in the newborn hph-1 mice (P<0.05).

**Conclusion:** Pulmonary hypertension is present from birth in the GCH1 deficient mice, not as a result of vasoc chromium, but secondary to pulmonary vascular remodeling.

**P3338**

**Autoimmunity and pulmonary arterial hypertension: The role of leptin**

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**Introduction:** p130 Cas kinase is a docking protein integrating and regulating extracellular cues and intracellular signaling pathways that controls cell proliferation and motility. Therefore, we hypothesize that p130 Cas contributes to excessive migration and proliferation of PA-SMCs in idiopathic Pulmonary Arterial Hypertension (iPAH).

**Methods:** Protein and phosphorylation levels of p130Cas were quantified by Western blot analyses. To assess the functional role of p130 Cas in iPAH and controls, we evaluated migration and proliferation of cultured PA-SMCs with and without p130Cas inhibition by siRNA.

**Results:** We observed significantly elevated p130 Cas protein expression and activity in iPAH patients compared to controls. In addition, decreasing p130 Cas signaling by RNA interference reduced to similar levels both the migration and proliferative potentials of iPAH and control PA-SMC. The decreased migration and proliferation are respectively mediated by decreased matrix metalloproteinase (MMP)-2 release and by decreased mitogen-activated protein kinase (MAPK) activation.

**Conclusions:** These results demonstrate that p130 Cas protein expression and activity induces PA-SMC proliferation and migration in iPAH, suggesting p130 Cas as an attractive drug target for PAH therapy.

**P3341**

**Ghrelin effects on local renin angiotensin from pulmonary vessels**

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**Methods:** Protein and phosphorylation levels of p3330 were quantified by Western blot analyses. To assess the functional role of p3330 in iPAH and controls, we evaluated migration and proliferation of cultured PA-SMCs with and without p3330 inhibition by siRNA.

**Results:** We observed significantly elevated p3330 protein expression and activity in iPAH patients compared to controls. In addition, decreasing p3330 signaling by RNA interference reduced to similar levels both the migration and proliferative potentials of iPAH and control PA-SMC. The decreased migration and proliferation are respectively mediated by decreased matrix metalloproteinase (MMP)-2 release and by decreased mitogen-activated protein kinase (MAPK) activation.

**Conclusions:** These results demonstrate that p3330 protein expression and activity in iPAH patients compared to controls. In addition, decreasing p3330 signaling by RNA interference reduced to similar levels both the migration and proliferative potentials of iPAH and control PA-SMC. The decreased migration and proliferation are respectively mediated by decreased matrix metalloproteinase (MMP)-2 release and by decreased mitogen-activated protein kinase (MAPK) activation.

**Background:** Published data sustain the participation of vascular rennin angiotensin system (RAS) on alteration of pulmonary vessels reactivity during the allergic airway inflamation. Ghrelin is a growth hormone-releasing peptide involved in modulation of immune function.
Objective: This study aims to investigate the interaction between ghrelin and local RAS from rat pulmonary vessels during ovulation – induced allergic airway disease.  

Methods: The angiotensinogen (AGT) – induced contractions were assessed on isolated pulmonary artery and veins from ovulation sensitized rats receiving either saline (OSG) or ghrelin (OSG) by endotracheal instillation. Experiments were performed in the absence or the presence of losartan, D-ALA7, chymostatin and N-nitro-L-arginine methyl ester (L-NAME).  

Results: The angiotensinogen (AGT) contractile effects mediated by AT1 receptors were diminished by 25% on vessels from OSG group. The D-ALA7 and LNAME significantly increases the AGT - induced contraction on OSG. The amount of nitric oxide released after stimulation with angiotensinogen (AGT) is higher on OSG and it is blocked by D-ALA7.  

Conclusion: Our results suggested that pulmonary delivery of ghrelin could modulate the local RAS from pulmonary vessels, probably by promoting the angiotensin 1-7 mediated effects. These data sustained the existence of an additional possible way for ghrelin’s beneficial effects on the lung.

P3342 Nestin expressing progenitor cells in pulmonary vasculature  

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Vascular smooth muscle cells (VSMCs) and pericytes (PCs), distinguished by the expression of neuronal stem cell marker “Nestin”, may represent stem cell-like progenitor cells for tissues in various organs. In one of our previous studies, we found that NPCs in both blood vessel and trabecular muscle vessels are the progenitors of testosterone producing Leydig cells.  

To analyze the expression pattern of nestin and its role as marker for proliferating progenitor cells in the lung, nestin expression and localization was investigated during postnatal development in nestin-GFP mice. To investigate nestin expression during vascular remodelling, samples from two models of pulmonary hypertension (PH) [monocrotaline (MCT) rat model and hypoxic mouse model] as well as human samples from patients of PH were analyzed. Nestin data was compared with expression of proliferation markers (PCNA, Ki67) and PDGF receptors.  

Nestin was found in a subpopulation of VSMCs and PCs of lung vasculature. As compared to adult normoxic controls significantly higher nestin expression was observed in pulmonary vasculature of postnatal tissues and in adult lungs between day 3-7 of hypoxic exposure but not at later time points when PH became evident. Increase of nestin correlated well with an increase of cell proliferation. In hypoxic lungs peak of phosphorylated (activated) PDGF receptor β correlated with nestin one. Increase of nestin-immunoreactive VSMCs and PCs was also found in MCT rat and human lungs. Certain contractile cells capable of proliferation could be identified by Nestin expression in lungs and may be used as prognostic marker and new target for therapeutic interventions of diseases like PH.

P3343 Endothelial cell mechanics are altered in pulmonary arterial hypertension (PAH)  

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Idiopathic pulmonary arterial hypertension (IPAH) and collagen vascular disease associated PAH (APAH) are associated with a significant elevation of inflammasome activation and release of IL-1β and IL-6 in patient plasma [1]. We hypothesized that these biochemical changes will affect intercellular force distribution in the constituent endothelial cells. To test this hypothesis, we applied a novel in vitro technique to cultured Human Lung Microvascular Endothelial Cell (HLMVEC), serum derived from IPAH and APAH patients, and measured subsequent changes in HLMVEC intercellular forces [2]. In comparison to time-matched controls (n=4), HLMVEC monolayers exposed to patient serum (n=7, APAH, n=8) were significantly more contractile (average contractile moment per monolayer: control cells = 153.5±13.5 pN/m, IPAH cells = 222.3±9.6 pN/m, and APAH cells = 223.8±22.8 pN/m), and exhibited greater number of intercellular mechanical stress hot-spots. Accordingly, we suggest that inflammasome mediated enhancements in endothelial intercellular forces may play an important role in decreased vascular compliance observed in PAH.  

References:  

P3344 Involvement of cytoskeletal protein Paxillin in the pathogenesis of pulmonary hypertension  

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Pulmonary arterial hypertension (PAH) is a fatal disease characterised by a pronounced remodelling of the pulmonary vasculature. The remodelling process entails deposition of the extracellular matrix (ECM) proteins, proliferation of pulmonary arterial smooth muscle cells (PASMC), and changes in the composition of cytoskeletal proteins. Paxillin is one of the most important cytoskeletal proteins, mediating protein-protein interactions and consequently modulating cell signalling. In this study we have investigated the contribution of Paxillin in vascular remodelling.  

In lungs of IPAH patients we detected enhanced Paxillin expression compared to controls on both mRNA and protein levels. Immunohistochimical analysis demonstrated expression of Paxillin in pulmonary vasculature and PASMC. Similarly, in the hypoxia mouse model of pulmonary hypertension, expression of Paxillin was localised to the vessels. Laser microdissection of intrapulmonary arteries revealed enhanced Paxillin expression in hypoxic lung vessels. Functional measurements were performed by silencing Paxillin expression. Paxillin knockdown caused changes in the phosphorylation status of Akt, and Erk1/2 leading to decreased cell viability, proliferation as well as increased apoptosis of human primary PASMC. Furthermore, immunohistofluorescence of PASMC revealed that Paxillin knockdown led to cytoskeletal alterations and impaired cell adhesion. Paxillin has previously been documented to be involved in cell spreading, migration, features characteristic of vascular remodelling. This is however the first report that indicates the involvement of Paxillin in vascular remodelling in the lung, and its association with human PAH disease.

P3345 Determination of cell-derived microparticles in patients with pulmonary hypertension and connective tissue disease using flow cytometry  

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Background: Microparticles (MPs) are small plasma membrane vesicles released from different cell types during activation or apoptosis. Increased MPs levels have been associated with cardiovascular diseases, thrombotic disorders and systemic inflammatory conditions. In pulmonary hypertension (PH) the role of MPs is poorly understood.  

Aims and objectives: The aim of this study was to analyze the MPs fractions in PH and connective-tissue disease (CTD) patients which represent a risk factor for PH development.  

Patients and methods: Plasma samples derived from PH and CTD patients were tested using flow cytometry (FC). Circulating MPs from platelets (CD61+), endothelial cells (CD31+) as well as Annexin V+ were measured by FC in 28 PH patients, 36 CTD patients and 41 healthy controls. The levels of MPs were compared in these three groups.  

Results: The overall fraction of MPs was higher in PH patients (57±26% of total events) and CTD patients (51±21%) as compared to controls (42±18%) (p<0.05). Platelet derived CD61+ MPs were tendentially increased in PH patients comparing to controls (p=0.096) whereas CD31 expression was not found to be different on MPs from patients and controls. The expression of Annexin V on MPs from PH patients were significantly higher as compared with controls (mean fluorescence intensities: 56±26% vs. 38±17% (p=0.003)). There were no significant differences between Annexin V expression levels on MPs in PH vs. CTD patients (p=0.384) and not between CTD vs. controls (p=0.179).  

Conclusions: According to these preliminary data, the plasma levels of Annexin-V+MPs are increased in PH patients and may be related to an activated pro-coagulatary and inflammatory vascular status.

P3346 The role of the accessory type III transforming growth factor-β receptors in the regulation of pulmonary vascular development  

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Pulmonary artery smooth muscle cell behaviour, including proliferation, apoptosis, and matrix production, is controlled by transforming growth factor (TGF-β), acting via two type II (Acrv1 and Tgfb1) and two type III (endoglin (Eng) and betaglycan (Tgfb3)) TGF-β receptors. Knockdown of TGFBR1 by siRNA in primary human pulmonary artery smooth muscle cells (PASMC) increased PASMC proliferation (3 fold; assessed by BrdU incorporation) in vitro, in a TGF-β independent manner. However, apoptosis rates of the PASMC were not affected by siRNA knockdown of TGFBR3. The siRNA knockdown of other TGF-β receptors, ACRV1, TGFBR1, TGFBR2 and ENG, did not impact TGF-β independent proliferation or apoptosis of PASMC. These data point to a novel, TGF-β independent role for TGFBR3 in regulating PASMC growth. This idea assumes importance considering that we
have also observed perturbed expression of TGFBR3 in the lungs of neonatal mice with hyperoxia (85% O₂)-induced lung injury, which results in bronchopulmonary dysplasia (BPD). The mRNA levels (assessed by quantitative real-time RT-PCR for TGFBR3 were downregulated (4.4-fold, p=0.003), while TGFBR3 protein levels were downregulated by 70%. Laser capture microdissection confirmed downregulated expression of TGFBR3 in the pulmonary vasculature of the developing mouse lung. Taken together, these data suggest a role for TGFBR3 in vascular smooth muscle cell function which could lead to a dysregulation of TGF-β signaling in the pulmonary vasculature, which in turn could contribute to the impaired pulmonary vascular growth and development associated with the lung hypoplasia observed in patients with BPD.

P3347 Elevated levels of adenosine in the lungs lead to chronic lung injury and pulmonary hypertension
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Pulmonary Hypertension (PH) is characterized by increased pulmonary vascular tone and remodeling of the pulmonary vasculature including muscularization of vessels. PH is often associated with underlying chronic lung diseases (CLD) such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). The adenosine (Ado) A2B receptor (R) expression is increased in patients with COPD and IPF. Activation of the A2B by Ado has been shown to regulate fibrosis through its action in inflammatory and structural cells. However, the role of Ado and the A2BR in the pathogenesis of PH is not known.

Hypothesis: Blockade of the A2B modulates the development of PH in CLD. Ado deaminase (ADA)-deficient mice have increased levels of Ado in the lung tissue that lead to CLD. On day 30, once lung injury was established, mice were provided with Chow containing placebo or GS-6201, an A2B antagonist, for the next 10 days. On day 41, right ventricle systolic pressure (RVSP), systemic blood pressure, heart rate and lung function measurements were performed. ADA-deficient mice had increased RVSP compared to control mice. Lung function measurements revealed increased airway resistance and a reduction in airway and tissue compliance in ADA-/- mice. Blockade of the A2BR by GS-6201 inhibited the increased RVSP and restored lung function. No change in systemic systolic blood pressure or heart rate was observed in mice treated with placebo or GS-6201. These results highlight the role of the A2BR in the pathogenesis of PH associated with elevated tissue Ado and CLD. The results suggest that targeting the A2BR could be a potential target for the treatment of PH secondary to CLD.

P3349 Antibiotics in exacerbations of asthma
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Introduction: Current guidelines explicitly do not recommend prescribing antibiotics for asthma exacerbations in order to avoid overprescription. We aimed to assess the prescription rate of antibiotics related to asthma exacerbations in primary care and which clinical patient characteristics are associated with antibiotic prescription.

Methods: We retrieved all electronic patient records concerning acute asthma in adults during 2008 recorded amongst 149,279 patient contacts by the centralised out-of-hours General Practice (GP) service in Amsterdam. Through univariate and multivariate analyses we analyzed the clinical parameters documented by GP’s of patients who received antibiotics.

Results: Of 540 identified exacerbations, 108 (20%) were treated with antibiotics, of which in 16 cases (15%) a prescription of pneumonia was documented. Univariate analysis showed that antibiotic prescription was positively associated with age (p=0.006) and clinical signs (Table 1). Multivariate analysis yielded a Nagelkerke R² of 0.331 for the variables age, ill appearance, spurn, tronchi and fever. Antibiotic prescription was not associated with other treatments of exacerbation.

Table 1. Clinical associates of antibiotic treatment

<table>
<thead>
<tr>
<th>History</th>
<th>p-value</th>
<th>Examination</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>0.002</td>
<td>Ill appearance</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum</td>
<td>&lt;0.001</td>
<td>Fever</td>
<td>0.023</td>
</tr>
<tr>
<td>Common cold</td>
<td>0.178</td>
<td>Rhonchi</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms of Bar</td>
<td>0.019</td>
<td>ENT-problems</td>
<td>0.650</td>
</tr>
<tr>
<td>Symptoms &gt; 3 days</td>
<td>0.261</td>
<td>Focal abnormalities on auscultation</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;0.001</td>
<td>Wheezing</td>
<td>0.086</td>
</tr>
</tbody>
</table>

Conclusion: Antibiotics are prescribed more often for asthma exacerbations by GPs than proposed by international guidelines. Fever appears to be a major trigger for antibiotic therapy, in contrast to recommended care. This suggests that overprescription of antibiotics for asthma exacerbations is prevalent.

P3350 Monitoring free serum IgE in severe asthma patients treated with omalizumab
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It is stated that benefit of omalizumab treatment in severe IgE-dependent asthma requires serum free IgE concentrations below 50 ng/ml. It is unclear if monitoring free serum IgE is clinically meaningful once omalizumab treatment is initiated. Free IgE and omalizumab serum concentrations were quantified in 22 patients with severe asthma (68% female, 47±11 yrs., mean ±(SD) pre-bronchodilator FEV₁ 62±13%, baseline mean ±(SEM) free serum IgE 652±136 ng/ml treated with omalizumab for 4 months using a Recovery-ELISA.

Omalizumab treatment reduced free serum IgE prior to the second omalizumab injection by 73%, after 16 weeks by 81% to 51±12 ng/ml (p=0.001 vs. baseline). 17 patients responded to anti-IgE therapy as judged by physician-rated global evaluation of treatment effectiveness. There was no relation between free serum IgE concentrations and treatment response. 41% of responders had free IgE levels above 50 ng/ml and 40% of non-responders had 50 ng/ml. There was no significant or clinically relevant difference regarding changes in lung function, exhaled NO, asthma control, and quality of life between patients with free IgE below or above 50 ng/ml.

Monitoring free IgE and omalizumab serum concentrations in patients treated with omalizumab does not predict clinical response or add to the decision to continue or...
**P3351**

**Serum immunoglobulin level is a useful marker for the risk of opportunistic infection in steroid dependent patients with chronic inflammatory airway diseases**

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**Aim:** Patients with chronic inflammatory airway diseases such as severe asthma, pulmonary fibrosis often need to have long-term oral corticosteroids (O-CS). Patients who are administered O-CS, even a small amount, are suggestive for opportunistic infections (OI). According to guidelines, prednisolone equivalent dose of 7.5 mg/day is considered as a GINA step 4/5 (Churg-Strauss syndrome) taking regular-use of O-CS were enrolled to this study. We retrospectively reviewed the medical records and collected the data about incidence of OI and serum IgG levels of the patients.

**Results:** Seven out of 17 patients suffered from OI. The average IgG level in patients with OI (623±154 mg/dl, n=7) was significantly lower than patients without OI (879±188 mg/dl, p-value<0.01). The area under the ROC curves was 0.87. The most reliable cut-off level was 725 mg/dl with specificity 89%, sensitivity 75%, positive predictive value 86% and negative predictive value 80%.

**Conclusion:** Serum IgG need to be monitored when patients were given O-CS. It is crucial to keep serum IgG levels more than 725 mg/dl to prevent OI.

**P3352**

**Effects of omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma**

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Allergic asthma is a chronic inflammatory airway disease in which immunoglobulin E (IgE) and eosinophils play important pathogenetic roles. We investigated the effect of the anti-IgE antibody omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma eligible for omalizumab treatment according to current guidelines. We conducted a prospective study with consecutive GINA step 4/5 patients (19 female, 48±11 yrs., 78±12 kg, 274±228 IU/ml total IgE, FEV1 at baseline 1.8±0.6 L, 61±8±19.5% pred.) omalizumab (median 450 mg/month) was administered s.c. as add-on therapy. Exhaled nitric oxide (NO), peripheral blood eosinophils and serum interleukin-5 were measured before and after 16 weeks of treatment. In all patients total daily doses of inhaled and oral corticosteroids remained stable during treatment.

23 (74%) patients responded to therapy (GETE). BASELINE NO was 43±8 ppb (mean±i-SEM) for responders (R) and 23±6 ppb for non-responders (NR), blood eosinophils were 3.9±0.7±0.07±0.05 (R) and 2.5±0.5±0.08±0.06 (NR), and IL-5 was 7.5±1.1±1.3 (R) and 1.9±1.3±0.3 (NR). After 16 weeks NO decreased by 3±6 ppb (P<0.004) and 12±18 ppb (NR, p=0.375), blood eosinophils were unchanged (R week0-week16: 0.01±0.06±0.01±0.06, p=0.99, and NR, p=0.66) and IL-5 decreased by 3±7±0.0±0.1 ng/m (P<0.001) and 0.3±1.4±0.3 (NR, p=0.62).

Patients, in a clinical response to omalizumab had higher pre-treatment serum IL-5 levels and a pronounced decrease in serum IL-5 following omalizumab. Blood eosinophils were unchanged, and exhaled NO was low prior and on treatment with omalizumab, consequent to high-dose ICS treatment.

**P3354**

**Reduction in incidence of exacerbations in patients with Alpha 1 antitrypsin deficiency (A1ATD) treated with concentrates of Alpha 1 antitrypsin (A1AT):**

REXA study

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**Introduction:** Augmentation therapy with plasma derived Alpha 1 Antitrypsin represents the only specific treatment for patients with Alpha 1 Antitrypsin Deficiency. The aim of this study was to demonstrate that augmentation therapy can reduce the number of exacerbations in patients with A1ATD.

**Material and methods:** Retrospective multicentric study. We included 127 patients who received augmentation therapy for 18 months and with clinical follow-up for 18 months before treatment. We compared the incidence of exacerbations into the two periods.

**Results:** 127 patients, 63% male, age:52y, former smokers:79.4%, never smok-ers:17.4%, FIZZ-93.6%. Basal FEV1:1.24L, (±0.5). Patients were treated with Protalast® (53.5%) or Tryster® (46.5%), 78% every 21 days. 52 days patients did not present exacerbations in pretreatment period. Augmentation therapy was associated with reduction of 2.4 exacerbations for every ten treated patients in total population and 6 exacerbations for every 10 treated patients in those with previous exacerbations.(Figure 1) Untreated patients have between 1.4 and 4 times more risk of exacerbation than treated patients. We didn't observe differences between both available A1AT products.

**Conclusions:** Augmentation therapy in the A1ATD reduces the total number of exacerbations with low frequency of adverse events. Study realized with Grifols support.

**P3355**

**Efficacy of rolflumilast in the frequent exacerbation COPD phenotype**

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**Background:** COPD exacerbations (EXs) are associated with increased morbidity, mortality and disease progression. The ECLIPSE study showed the best predictor of future EXs is a history of EXs, identifying a frequent exacerbator phenotype maintained over time. Rolflumilast (ROF) reduces EX rate in frequent exacerbators, but its relative effect in this phenotype is not known.

**Methods:** In a post-hoc pooled analysis of two 1-yr studies of ROF 500g in pts with severe COPD, chronic bronchitis and a history of EXs, pts were classified as frequent (≥2 events) or infrequent (1 event) exacerbators based on moderate/severe EX history in the previous yr. EX frequency status was analysed in ROF- and placebo-(PBO)-treated pts at baseline and at yr 1.

**Results:** Among ROF-treated frequent exacerbators (n=413), 32.0% still had frequent EXs at yr 1 vs 40.8% of PBO-treated pts (n=417; RR=0.799, p=0.0148). Among infrequent exacerbators, 17.5% of ROF-treated pts (n=1124) had ≥2 EXs at yr 1 vs 22.9% of PBO-treated pts (n=1137; RR=0.768, p=0.0018). This reduction was similar when considering concomitant LABA, previous ICS treatment or severe EXs leading to hospitalisation/death. When analysed by COPD severity, 26.4% of ROF-treated frequent exacerbators with severe COPD (FEV1 ≤30–50% pred., n=246) still had frequent EXs at yr 1 vs 38.9% of PBO-treated pts (n=239; RR=0.683, p=0.0042); the percentage of frequent exacerbators was substantially lower between severe and moderate COPD (FEV1 ≥50%).

**Conclusions:** This analysis shows that ROF shifts pts from the frequent to the more stable infrequent exacerbator state. This effect was not seen in frequent exacerbators with very severe COPD, highlighting the need for early treatment initiation.

**P3356**

**Modelling and simulation in successful drug development programmes:**

**Characterisation of exacerbation reduction with rolflumilast to corroborate the importance of defining patient subsets in COPD**

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**Background/Rationale:** Rolflumilast (ROF), an oral, selective PDE4 inhibitor, reduces the rate of exacerbations and improves lung function in severe COPD. During clinical development, modelling and simulation techniques were used to identify and confirm a paradigm to explore patient, disease and treatment covariates. This approach identified patient populations that will benefit most from ROF, and was used to help design confirmatory clinical trials.

**Methods:** Data from two 1-year, randomised, double-blind, placebo-controlled, parallel-group trials [Rennard S, et al. Respir Rev 2011;12(1):1] in 2686 patients were used to build exacerbation and lung function models to identify patient characteristics that significantly impacted the clinical endpoints.

**Results:** Patients with chronic bronchitis, higher cough/sputum scores, concomi-tant ICS use and low predicted FEV1 at baseline were identified as having a higher rate of exacerbations and treatment effect. Patient characteristics as defined by the models were used, in addition to a history of exacerbations, to simulate the design of two other 1-year clinical trials [Calverley PMA, et al. Lancet 2009;374:685–94].
Conclusions: paβ reduced the frequency of exacerbations in individual patients in active therapy group than that in placebo group (37.0% vs. 63.0%, p<0.05). The percentage of concomitant antibiotics was significantly lower in OM-85 BV group than in placebo group (27.9% in BV group vs. 27.7% in placebo group, p<0.05). There was no significant difference between the two groups in the incidence of adverse events (27.9% in BV group vs. 27.7% in placebo group, p>0.05).

P338

Efficacy and safety of bacterial lysates in patients with chronic obstructive pulmonary disease and exacerbations

Hao Tang, Zheng Fang, Qingyu Xiu, on behalf of the Broncho-Vaxom Study

Objective: To study the effect of paβ-blockers on exacerbations of COPD exacerbation requiring hospitalization. To each case, controls were matched on age, sex and indexdate. Cox proportional hazard and conditional logistic regression analyses were used.

Results: Within the cohort of 6788 COPD patients, 619 patients had a COPD exacerbation requiring hospitalisation. Current use of paβ-blockers significantly reduced the risk of severe COPD exacerbation in the cohort analysis (HRadj 0.73, 95%CI 0.60-0.90). In the case-control analysis, use of paβ-blockers reduced the risk of exacerbations by 40% (ORadj 0.60, 95% CI 0.44-0.82). When controlling for confounding by indication, the protective effect was clearly attenuated (ORadj 0.87, 95% CI 0.52-1.45). In patients with co-existing heart failure, a significant protective effect was observed (ORadj 0.15, 95% CI 0.03-0.80).

Conclusions: The choice of study design is crucial when assessing the effect of paβ-blockers on COPD outcomes.

P3360

Skin sensitivity to corticosteroids is associated with COPD susceptibility

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Introduction: Inhaled corticosteroids (ICS) improve symptoms, exacerbation rates and quality of life in COPD. However, not all COPD patients benefit from ICS treatment. Corticosteroid sensitivity can be tested with the skin blanching test, where topical corticosteroids cause local vasoconstriction. We investigated in young and old individuals if skin response to corticosteroids is associated with susceptibility to develop COPD.

Methods: Young (18 – 40 years) healthy subjects who were non-susceptible or susceptible to develop COPD (n=9 and 14 resp.), and older (40-75 years) subjects without and with COPD (n=15 and 47 resp.) were included. Susceptibility in young subjects was based on a high prevalence of COPD in smoking family members of these subjects. Budesonide dissolved in 95% ethanol was applied to the skin in eight concentrations (0-1000 μg/ml). Blanching was scored with a 7-point scale: 0 (no blanching) and 3 = intense blanching.

Results: Young non-susceptible subjects showed higher blanching scores compared to all groups (figure 1). In COPD patients, a lower blanching score correlated with lower FEV1/FVC ratio (B=-0.07, p<0.01) and higher GOLD stage (figure 2).

Conclusions: These preliminary data suggest that relative corticosteroid insensitivity contributes to COPD development and progression.

P3359

β-blockers and risk of COPD exacerbation requiring hospitalisation in patients with COPD

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1Medical Informatics, ErasmusMC, Rotterdam, Netherlands; 2Department of Respiratory Diseases, University of Ghent, Ghent, Belgium

Background: In the past, β-blockers were contra-indicated in COPD. Recent evidence, including a cohort study by Rutter et al. (Arch Intern Med 2010), suggests that β-blockers produce good outcomes in COPD. This degree of protection might be biased.

Objectives: To study the effect of β-blockers on the risk of severe COPD exacerbations.

Methods: We conducted several analyses to study the effect of β-blockers on COPD exacerbations by: 1 mimicking the cohort design of Rutter 2 avoiding immortal time and exposure bias through a nested case-control study in a COPD cohort and 3) reducing confoundings by indication by restricting the case-control analyses to users of β-blockers during follow-up. Data from the Dutch IPCI OP database (2000 to 2007) were used. Cases were all COPD patients who had a first COPD exacerbation requiring hospitalization. In each case, controls were matched on age, sex and indexdate. Cox proportional hazard and conditional logistic regression analyses were used.

Results: Within the cohort of 6788 COPD patients, 619 patients had a COPD exacerbation requiring hospitalization. Current use of β-blockers significantly reduced the risk of severe COPD exacerbation in the cohort analysis (HRadj 0.73, 95%CI 0.60-0.90). In the case-control analysis, use of β-blockers reduced the risk of exacerbations by 40% (ORadj 0.60, 95% CI 0.44-0.82). When controlling for confounding by indication, the protective effect was clearly attenuated (ORadj 0.87, 95% CI 0.52-1.45). In patients with co-existing heart failure, a significant protective effect was observed (ORadj 0.15, 95% CI 0.03-0.80).

Conclusions: The choice of study design is crucial when assessing the effect of β-blockers on COPD outcomes.

Figure 1

Figure 2

P3361

Inhaled corticosteroids in patients with mild to moderate COPD with and without airway hyperresponsiveness to mannitol: A randomized placebo controlled trial

Andreas Scherr1, Joehann Anja2, Schaffroth Salome3, David Miedinger2, Maur Sabrina2, Anne Taegtmeier2, Chajed Frashuti3, Sandra Anderson3, Tamim Michael1, Jörg Daniel Leuppi4, 1Clinic of Respiratory Medicine, University Hospital Basel, Basel, Switzerland; 2Clinic of Internal Medicine, University Hospital Basel, Basel, Switzerland; 3Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, Australia

Background: Based on former data airway hyperresponsiveness (AHR) to mannitol challenge could allow to identify a subgroup of subjects who will respond to treatment with ICS.

Methods: We investigated 68 subjects with mild to moderately severe COPD. All subjects were treated with tiotropium initiated 4 weeks prior to randomisation. Subjects were randomized to either budesonide (daily dose of 1600 mcg) or placebo for 3 months. At all visits lung function, quality of life (SGRO), AHR to mannitol, exhaled nitric oxide (NO) and MRC were assessed. AHR was defined as a 15% fall in FEV1 at < or = to 6.35 mg (PD15). RDR was calculated as the percent fall in FEV1 at the last dose divided by totally dose of mannitol administered.

Results: There was no significant change from baseline of FEV1% pred. (2.46 95% CI [-1; 5.9] p= 0.162), quality of life (SGRO) (3.2 95% CI [-8.5; 21] p= 0.227), nitric oxide (-5.48 95% CI [-11.2; 0.2] p=0.058) and MRC (0.4 95% CI [-2.9; 0.5] p=0.258).

Conclusions: These preliminary data suggest that relative corticosteroid insensitivity contributes to COPD development and progression.
Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using HRCT and lung function tests

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The aim of this study was to assess the acute effect of inhalation of budesonide/formoterol combination and placebo using lung function tests and imaging in COPD patients and to compare both. A total of 10 patients was assessed in a double blind cross over study. Airway volumes were analysed using segmentation of the HRCT images. Results showed that distal airway volume significantly increased in patients four hours after receiving budesonide/formoterol combination. No other lung function parameters showed a significant change. When considering the effect of placebo a significant decline in distal airway volume and peak expiratory flow was observed. A downward trend was depicted by forced expiratory volume in one second. The bodyplethysmography showed a significant increase in specific airway resistance. In addition it was shown that imaging was the only parameter that was able to predict correctly the visit at which the combination product was administered for all patients.

Antibiotic prescription in asthma exacerbations in the admitting and discharged patients (A&E) department

Caroline Gouder, Justine Farrugia Preca, Rachelle Asciaj, Josef Micallef, Stephen Montefort. Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta

Aim: To assess the appropriateness of antibiotic prescription in patients diagnosed with asthma exacerbations in the A&E department. Methods: Patients presenting at the A&E department over 10 consecutive months (January to October 2010) were included in a prospective study. Comparative statistical analysis was carried out using the t-test. Results: A total of 244 patients were included. Forty-eight patients (19.7%) had been prescribed antibiotics by their general practitioner prior to presentation to A&E. A chest X-ray was done in 201 patients (82.4%). A radiological suggestive of pneumonia was reported in 12 patients (6%). A white cell count (WCC) was available in 165 patients (67.6%). Antibiotics were prescribed in 30.2% had a raised WCC (mean 10.42×109/L), 23% were febrile at admission and 7.6% had a raised temperature at admission. A radiological infiltrate suggestive of pneumonia was reported in 12 patients (6%). A white cell count (WCC) was available in 165 patients (67.6%). Antibiotics were prescribed in 30.2% (n=50; CI 95% 24.1-36.4) of patients and to compare both. A total of 10 patients was assessed in a double blind cross over study. Airway volumes were analysed using segmentation of the HRCT images. Results showed that distal airway volume significantly increased in patients four hours after receiving budesonide/formoterol combination. No other lung function parameters showed a significant change. When considering the effect of placebo a significant decline in distal airway volume and peak expiratory flow was observed. A downward trend was depicted by forced expiratory volume in one second. The bodyplethysmography showed a significant increase in specific airway resistance. In addition it was shown that imaging was the only parameter that was able to predict correctly the visit at which the combination product was administered for all patients.

This study showed that imaging is a sensitive, complementary tool to describe changes in airway structure and function. Future uses could include the assessment of anti-inflammatory compounds as standard lung function test might lack the sensitivity to describe the more subtle changes.

Antibiotic prescription in asthma exacerbations in the admitting and discharged patients (A&E) department

Caroline Gouder, Justine Farrugia Preca, Rachelle Asciaj, Josef Micallef, Stephen Montefort. Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta Department of Medicine, Mater Dei Hospital, Birirkara, Malta

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Non-tuberculous mycobacteria pulmonary infections

378. Non-tuberculous mycobacteria pulmonary infections

392. Geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples in Croatia

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Background: The incidence of non-tuberculous mycobacteria (NTM) as human pathogens is increasing. It has become clear that the NTM species obtained from clinical specimen differ strongly by region. Aims and objectives: To determine the distribution of NTM species obtained from pulmonary samples of individuals from different geographic regions in Croatia. Methods: Retrospective analysis on all NTM identified at the National Laboratory for Mycobacteria in 2007-2009. For each isolate the person's birth year, sex, specimen collection date, source and geographic region (cultural or sputum) were recorded. Microbiological criteria of the ATS/IDSA were used for a laboratory-based definition of pulmonary NTM. Results: NTM species were isolated from 712 individuals. 56% of isolates came from male (median age 62 y) and 44% from female (median age 64 years) individuals. More than two thirds of all isolates (525) originated from persons from the inland area. Of those 525 samples, 80 (15.2%) met the pulmonary NTM criteria, compared to 68 (36.4%) out of the 187 samples identified in the coastal area (p<0.0001). More than 90% of isolated species with insignificant clinical relevance originate from the inland area. Incidence of species with relevant clinical burden was significantly higher in the coastal compared to the inland area. Conclusions: The majority of all NTM isolates originated from the inland area. However, isolates which met the ATS pulmonary disease criteria were more frequently isolated from persons living in the coastal area. There, more than one third of all isolates likely represented true disease. Geographic region plays an important role for colonization or infection with NTMs in Croatia.
Nontuberculous mycobacteria – Isolation in respiratory specimens and its clinical relevance

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Background: Nontuberculous mycobacteria (NTM) isolation have been increasingly described, particularly in developed countries. Few studies in Portugal characterize and report its clinical relevance.

Aim: Characterize NTM isolated from respiratory samples between 2007-2010 at our center.

Methods: Retrospective analysis of patients followed in our hospital with NTM isolation in at least one respiratory specimen.

Results: NTM were isolated in 108 samples, 68 patients; mean age: 53.5±17.0 years; 63.6% male. Fourteen (20.6%) had HIV, eight with AIDS. Prior respiratory disease was present in 63.2% of patients, most frequently bronchiectasis (14; 32.5%), tuberculosis sequelae (11; 25.6%) and COPD (7; 16.3%). Eleven (26%) had mycobacterium avium complex (MAC), including M. avium and M. intracellulare (7; 39.7%) and M. gordonae (23,33%).

Discussion: M. gordonae was isolated in much higher frequency than that described in literature, unexplained by introduced NOTM species or by potential significant. When compared to MAC, it caused disease in 2 cases. NTM isolation didn’t relate to lung disease in 67.6% of cases. We found a statistically significant association between illness and MAC isolation. Further studies are needed to describe NTM and its clinical significance.

Pulmonary disease caused by non-tuberculous mycobacteria. Descriptive study and comparison with mycobacterium tuberculosis

Sandra Pedro Tejada1, Marcia Alfonso Imicon1, Bogota Vilar Azahabal2, Luis Miguel Sorria Riendas1, Nuria Marina Malanda1, Ines Martinez Rienda2, Israel Lopez Mirones1, Jose Maria Antohual1, Elena Urra Zalbidigoeitia2, Rafael Zacalan Jorge1, 1Pneumology, Cruces Hospital, Barakaldo, Spain; 2Microbiology, Cruces Hospital, Barakaldo, Spain

Aims: To describe the epidemiological, clinical and radiological data of pulmonary disease (PD) caused by non-tuberculous mycobacteria (NTM) diagnosed in a period of 12 years in an area of Vizcaya, and to compare the incidence with the cases of M. tuberculosis (MT).

Material: We reviewed all cases of PD caused by mycobacteria between 1997-2008 in our center, attending a population of 420.000. The diagnosis of NTM PD was conducted according to criteria of ATS.

Results: We found 1019 cases of PD caused by mycobacteria,788 (77.3%) for MT and 231 (22.7%) NTM. 216 M. kanssaii (MK), 1 M. avium complex (MAC), 2 M. abscessus, 1 M. xenopi and 1 M. celatum. NTM PD was more frequent in men (73.2%) and the mean age was 53.9±5.2 years. 7% of patients with MK and 9.1% of patients with MAC had extra pulmonary affection. 36 patients affected HIV coinfection. The annual incidence rate/100.000 of MT infection had the highest peak in 1999 with 22.8 and the lowest in 2008 with 11.5. The highest rate of NTM infection was in 1998 (74.4) and was lowest in 2008 (1.2). The incidence of PD by NTM and MT had a descending tendency in the 12 years studied, which is more remarkable since 2005.

High burden of rapidly growing non-tuberculosis mycobacteria in patients with respiratory disease undergoing elective bronchoscopy

Neranjani Dissanayake1, Dushmantha Madegedara2, Dhammika MagamaArachchi2, Udani Kanarathna2, Duminda Yasaratne2, Chathuranga De Silva2, Chandana Chinthana2, Samadara Nakandala2, Prasanne Wijerathne2, Chathura Wirasinghe1, 1 Respiratory Disease Treatment Unit, Teaching Hospital, Kandy, Sri Lanka; 2 Department of Cell Biology, Institute of Fundamental Studies, Kandy, Sri Lanka

Background: Pathogenicity of pulmonary non-tuberculous Mycobacteria (NTM) is less well understood than that of M. tuberculosis (MTB) complex. Both will show identical results on acid-fast staining (AFS), but culture characteristics are commonly used for differentiation in the local setting.

Objective: To assess the pattern of mycobacterial culture among patients with respiratory illness and negative sputum for AFS, in a pulmonary tuberculosis (PTB) prevalent environment.

Method: Bronchoalveolar lavage samples from 120 patients were inoculated onto solid media (Lowenstein-Jensen and Middlebrook 7H-10) at 280° and 37°C, in both light and dark conditions. All patients were negative for sputum AFS. Indicators for bronchoscopy were bronchiectasis, cavitatory lung disease and smear negative PTB.

Results: 67 patients yielded positive colonies within 8 weeks. 37 colonies were positive for AFS, of which 21 were rapidly growing Mycobacteria (RGM; <7 days) and 6 were slowly growing Mycobacteria (>7 days). Rapid colony growth strongly favours towards NTM. PCR based restriction fragment length polymorphism analyses on NTM are in progress. Concomitant sterile water, instrument cleaner fluid and saline samples did not yield culture growth.

Conclusion: We observed a high prevalence (>25%) of RGM in the study population. This raises major concerns on possible over-diagnosis of PTB leading to inappropriate therapy and false categorization of patients, in limited resource settings where sputum AFS results play a central role in managing PTB in clinical practice.
difference was seen in the clinical course of MAC whether or not steroid was administered for IP.

3398

Transitional change of the relationship between clinical efficacy of treatment for pulmonary MAC disease and drug-sensitivity test for MAC isolated Yoshihiro Kabashi, Masaaki Abe, Keiji Mouri, Yasushi Obase, Naoyuki Miyashita, Mikio Oka. Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan


Materials and methods: The subjects consisted of 60 patients who satisfied the diagnostic criteria of ATS and received the combination therapy using RPF, EB, SM and CAM. We divided into the former period (24 patients) and the latter period (36 patients).

Results: The average administration dose of CAM has been increased from the former period (800mg/day) to the latter period. Sputum conversion rate has been increased from 63% in the former period to 83% in the latter period. Clinical improvement has been increased from 38% in the former period to 53% in the latter period. The causative microorganisms isolated were M. avium in 35 patients and M. intracellulare in 25. There were no significant differences in the sputum conversion rate, clinical improvement, and drug-sensitivity test between M. avium and M. intracellulare in both periods. The isolated M. avium showed excellent drug-sensitivity to CAM and RPF in both periods. Regarding the relationship between clinical efficacy and MICs of RPF, EB, CAM, and SM, there was a good relationship only for CAM in both periods.

Conclusions: The good clinical effect has been obtained with the increase dose of CAM in the latter period. Because there was no significant difference in the result of drug-sensitivity test for isolated MAC in both periods, we speculated that the increase of administration dose of CAM has been influenced the good clinical effect in both periods.

379. Early wheezing conditions in childhood

3400

Association of wheezing phenotypes in the first 7 years of life with fractional exhaled nitric oxide and lung function in adolescence. The ALSpac study Licensez N, Duggal J, Jonathan A, Hogg J, John A. Henderson. 1Department of Community Based Medicine, University of Bristol, Bristol, United Kingdom; 2Department of Social Medicine, University of Bristol, Bristol, United Kingdom

Background: Patterns of wheezing during early childhood are associated with lung function and bronchial hypersensitivity in mid childhood. Little is known about the associations of early wheezing phenotypes with fractions of exhaled nitric oxide (FeNO), a marker of allergic airway inflammation, and lung function in adolescence.

Methods: This study was based on 6,841 children in a population-based prospective birth-cohort study. Latent class analysis identified 6 wheezing phenotypes (never/infrequent, transient early, prolonged early, late, persistent) based on wheezing patterns from birth to 7 years. FeNO levels and airway function (forced expiratory volume in 1 s (FEV1), forced expiratory volume ratio (FEV1/FVC), mid forced expiratory flow (FEF25-75)) were measured at age 15.

Results: Intermediate onset wheezing (18 months) was the most strongly associated with increased FeNO levels (ratio geometric means 2.01, 95% confidence interval: 1.63, 2.48), compared with the reference group never/infrequent wheezing. Wheezing phenotypes were not associated with FEV1, but showed associations with decreased levels of FEV1/FVC and FEF25-75 (most strongly for persistent wheezing: mean difference −0.50 (−0.62, −0.38) and −0.42 (−0.54, −0.29), respectively).

Conclusions: Wheezing phenotypes with onset after the age of 18 months and persistent wheezing were the most strongly associated with FeNO levels and lung function, respectively, in adolescence. Our results suggest that specific patterns of asthma-related symptoms in early life are associated with markers of lung morbidity at older ages.

3401

International study of wheezing in infants (EISL): How latitude modifies the association between risk and protective factors for recurrent wheeze during the first year of life

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Background: The influence of latitude on the strength of the association of risk/protective factors of recurrent wheeze (RW) has never been reported.

Methods: The “Estudio Internacional de Sibilancias en Lactantes” (EISL) included 30,093 infants 12 to 15 months of age, recruited from 13 Latin American centres (30,093.030) and from 5 European centres (n=5,063). Adjusted odds ratios (aORs) of factors associated to RW reported previously were used to build a meta-regression between the strength of the aORs of each factor and centre latitude (distance from equator either N or S). The meta-regression was further adjusted for continent and the slope expressed as adjusted regression coefficient (aβC).

Results: We found significant correlations between latitude (the higher the distance from equator the higher the strength of the association) and the magnitude of the aOR between RW and: 1. Cold(s) in the 1st 3 months (aβC =0.19; p=0.004); 2. Nursery school (aRC +0.25; p=0.01); 3. Siblings (aRC +0.024 for additional sibling; p=0.002); and 4. Breast feeding ≥3 months: the higher the latitude the higher the protection (aRC -0.17; p=0.047). Heterogeneity of the strength of aORs between centres was: 73.9% for colds, 67.1% for nursery school, 59.7% for siblings and 22.4% for breast feeding. Latitude explained (by R-squared) much of heterogeneity: 66.1% for colds, 54.9% for nursery school, 83.1% for siblings and 100% for breast feeding.

Conclusion: The magnitude in which some risk or protective factors are associated to recurrent wheeze during the first year of life varies significantly with latitude.

3402

The effect of late preterm birth on longitudinal lung spirometry in children Sarah J. Kotecha1, W. John Watkins2, David Herrick3, Shantini Paranjopyth4, Frank D. Dunstan2, A. John Henderson1, Sailesh Kotecha1. 1Department of Child Health, School of Medicine, Cardiff University, Cardiff, United Kingdom; 2Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, United Kingdom; 3School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom

Introduction: Rates of preterm birth have increased in most industrialised countries (Goldenbergh, R.L. et al. Lancet 2008; 371:75-84) but data on later lung function of late preterm birth is limited.

Aims and objectives: To compare lung function at 8-9 and 14-17 years in a population-based cohort of children born at 25-32, 33-34 and 35-36 weeks gestation with similar aged children born at term (≥37 weeks gestation).

Methods: From the Avon Longitudinal Study of Parents and Children (ALSPAC, n = 14062), children who had spirometry at 8-9 (n=6712) and/or 14-17 (n=4513) years of age were divided into 4 groups: 25-32, 33-34, 35-36 and ≥37 weeks (term) gestation.

Results: At 8-9 years of age, all spirometry measures (except FVC, in the 25-32 weeks gestation group) were significantly lower in both 25-32 and 33-34 weeks gestation groups compared to term controls (FEV1, mean s-score ± SD -0.46±0.876, -0.498±1.09 and 0.011±1.00 respectively). The 35-36 weeks gestation (FEV1, 0.008±0.008) and term groups had similar values. At 14-17 years of age, most spirometry measures in the 25-33 and 33-34 weeks gestation groups were not different from term controls except lower FEV1, FEF25-75 and FEF25-75/FVC in both 25-32 and 33-34 weeks gestation groups and lower FEV1/FVC in the latter group.

Conclusions: Children born at 33-34 weeks gestation have significantly lower lung function values at 8-9 years of age similar to decrements observed in the 25-32 weeks group although most of these differences were reduced by 14-17 years of age.

3403

Reduced neonatal lung function and wheezing illnesses during the first 5 years of life

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Introduction: Studies about reduced neonatal lung function and wheezing illnesses in childhood showed conflicting results. No study analyzed the association between the single occlusion technique (SOT) and wheezing illnesses during the first 5 years of life.

Objectives: The aim was to assess the association between resistance and compliance of the respiratory system (Rrs, Crs) measured shortly after birth and wheezing-associated primary care consultations during the first 5 years of life, different wheezing phenotypes, and asthma at age 5.

Methods: Infants participate in WHISTLER, a birth cohort on wheezing illnesses. SOT was performed during natural sleep before 2 months of age. Wheezing-associated consultations were collected from the electronic patient file. Poisson regression was used to study the association between Rrs and Crs and the number of consultations. Median Rrs and Crs values of children with different wheezing phenotypes and with and without asthma were compared by non-parametric tests.
**Results:** 549 infants had successful SAT and complete medical files. Every kPa/l/s increase in Rrs was associated with 9% more consultations in the first 3 years of life. Every cPcl/kg increase in Crs was associated with a 17% reduction of consultations in the first 3 years of life and 29% in the 4th-5th year of life. Children with late-onset or persistent wheezing and with asthma had significantly lower Crs values than their peers.

**Conclusion:** An increased neonatal Rrs is associated with more wheezing illnesses during infancy, while a reduced neonatal Crs is associated with more wheezing illnesses during the first 5 years of life, a late-onset or persistent wheezing phenotype, and asthma at age 5.

### Table: Association between BF and ADC, FRC, and TLC*

<table>
<thead>
<tr>
<th>ADC (cm²/second)</th>
<th>BF ≤ 3 months</th>
<th>BF &gt; 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-asthmatic mothers</td>
<td>0.094, 0.099</td>
<td>0.003, 0.012</td>
</tr>
<tr>
<td>Asthmatic mothers</td>
<td>0.003, 0.004</td>
<td>0.006, 0.009</td>
</tr>
<tr>
<td>FRC (litr)</td>
<td>0.016, 0.017</td>
<td>0.015, 0.019</td>
</tr>
<tr>
<td>Non-asthmatic</td>
<td>2.185, 0.912</td>
<td>0.500, 0.750</td>
</tr>
<tr>
<td>Asthmatic mothers</td>
<td>0.300, 0.437</td>
<td>0.372, 0.432</td>
</tr>
<tr>
<td>TLC (litr)</td>
<td>0.075, 0.050</td>
<td>0.142, 0.295</td>
</tr>
<tr>
<td>Non-asthmatic</td>
<td>4.569, 0.457</td>
<td>0.096, 0.096</td>
</tr>
<tr>
<td>Asthmatic mothers</td>
<td>4.245, 0.921</td>
<td>0.045, 0.288</td>
</tr>
</tbody>
</table>

\*Adjusted for age, height, sex, atopy, and parental asthma.

**Elevated FeNO (≥27 ppb, i.e. the highest quartile) was associated with maternal asthma, and increased airway responsiveness, but not with atopy, eosinophilia, or lung function.**

### Table: Parameter Adjusted OR# 95% CI p-value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR#</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal history of asthma</td>
<td>3.2</td>
<td>1.3, 8.1</td>
<td>0.012</td>
</tr>
<tr>
<td>Atopy</td>
<td>0.4</td>
<td>0.1, 1.1</td>
<td>0.064</td>
</tr>
<tr>
<td>Height</td>
<td>1.0</td>
<td>1.0, 1.2</td>
<td>0.252</td>
</tr>
<tr>
<td>PD&lt;sub&gt;40&lt;/sub&gt; V&lt;sub&gt;max&lt;/sub&gt;F&lt;sub&gt;RC&lt;/fsub&gt; ≤ 0.30 mg</td>
<td>4.1</td>
<td>1.4, 12.7</td>
<td>0.012</td>
</tr>
<tr>
<td>0.31-0.90 mg</td>
<td>1.4</td>
<td>0.4, 4.7</td>
<td>0.547</td>
</tr>
<tr>
<td>&gt; 0.91 mg</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\# Adjusted for maternal history of asthma, atopy, height, and PD<sub>40</sub> V<sub>max</sub>F<sub>RC</fsub>.

In conclusion, maternal history of asthma, and increased airway responsiveness are associated with elevated FeNO in symptomatic infants.

### Table: Association between early life exposure to PM<sub>10</sub> and lung function measurements at school-age

<table>
<thead>
<tr>
<th>PM&lt;sub&gt;10&lt;/sub&gt; μg/m&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30 mg</td>
<td>2.85</td>
<td>0.005</td>
</tr>
<tr>
<td>0.91 mg</td>
<td>3.26</td>
<td>0.008</td>
</tr>
</tbody>
</table>

\*Adjusted for sex, age, height, weight, prematurity, breastfeeding, heating, cooking, smoking exposure, parental education, type of respiratory illness, and family education level.

**Conclusions:** These results suggest that long-term exposure to PM<sub>10</sub> is associated with lower forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) at school-age. Future studies with larger samples are needed to confirm these findings.

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**References:**

1. Dogan D, Marjukainen P, Mäkelä M, et al. Elevated FeNO (≥27 ppb) is associated with maternal asthma, and increased airway responsiveness, but not with atopy, eosinophilia, or lung function.
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5. Dogan D, Marjukainen P, Mäkelä M, et al. Elevated FeNO (≥27 ppb) is associated with maternal asthma, and increased airway responsiveness, but not with atopy, eosinophilia, or lung function.
Late-breaking abstract: Comparison of bone marrow derived-mononuclear cells with mesenchymal stem cells on inflammatory and remodeling processes in experimental chronic allergic asthma

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Recently, we demonstrated the beneficial effects of bone marrow-derived mononuclear cells (BMDMCs) on lung morphofunction in experimental chronic allergic asthma. Mesenchymal stem cells (MSCs) have the potential to serve as a universal source for replacement of specific cells in several diseases and thus may offer hope as a potential therapeutic intervention for the treatment of the chronic remodeling changes that occur in asthma. This study aimed to compare the therapeutic effects of BMDMCs with MSCs on inflammatory and remodeling processes in experimental chronic allergic asthma. Thirty-six C57BL/6 mice were assigned to two groups. In the BMDMC group, mice were sensitized and repeatedly challenged with ovalbumin. Control mice (C) received saline under the same protocol. C and OVA groups were further randomized to receive saline (SAL), BMDMCs or MSCs (1×10^6) intratracheally 24 h after the last challenge. After one week, airway resistance, viscoelastic pressure, static elastance, as well as the degree of lung inflammation and remodeling (light microscopy and immunohistochemistry) were analyzed. BMDMC and MSC therapies led to a reduction in eosinophil infiltration and fibrosis in airway and lung parenchyma compared to OVA leading to a reduction in airway resistance and viscoelastic pressure. These parameters were more reduced after BMDMCs compared to MSCs. In conclusion, the present model of chronic allergic asthma, both BMDMC and MSC therapies were effective at modulating the inflammatory and fibrogenic processes, however, BMDMC administration led to greater beneficial effect.

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Late-breaking abstract: Changes in cortisol levels in the plasma of asthmatic individuals undergoing allergen challenge differentiation isolated early from dual responders

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Allergen inhalation challenge in mild asthmatic subjects induces airflow obstruction, airway hyperresponsiveness and inflammation, and provides a model for hypothesis-generating experiments to understand molecular regulation of these responses. Adult asthmatic subjects (18-55 years of age, with stable, mild allergic asthma, n=14) underwent cat allergen inhalation challenges. All subjects had an early asthmatic response of ≥20% fall in FEV1, and six individuals also had a late phase response of ≥15% fall in FEV1 (dual responders). Blood samples were collected just prior to, and two hours after allergen challenge. We have evaluated the differential changes in gene expression in peripheral blood cells and changes in the plasma metabolome, post-challenge compared to pre-challenge. Amongst other findings, we have demonstrated significantly reduced cortisol levels in the plasma of mild asthmatic subjects post-challenge, compared to pre-challenge (p=0.013). Importantly, this reduction in plasma cortisol was only significant in subjects who had an isolated early asthmatic reaction, rather than in subjects who also went on to develop a late phase asthmatic reaction. Interestingly, this is consistent with gene expression data demonstrating that in isolated early responders only, there is a significant increase in RNA transcript levels for the hydroxysteroid (11-beta) dehydrogenase 2 gene (HSD11B2), post-challenge compared to pre- (p=0.026). The HSD11B2 enzyme converts cortisol to inactive cortisone. Thus, allergen inhalation challenge may improve understanding of pathways and underlying genes associated with asthma.

Conclusion: IL-17 levels and PB neutrophil chemotaxis were increased in allergic patients challenged with DP. IL-17 is significant regulating neutrophil chemotaxis in patients with AR and AA.
Results: Neutrophil apoptosis before and after BAC was more intensive in HI group compared to patients with AR and AA (table). Neutrophil apoptosis in AA group was more inhibited after BAC in comparison with AR group. Conclusion: The preliminary results showed that neutrophil apoptosis was decreased in patients with AA and AR compared to HI before and after BAC. This finding lets us suggest, that specific allergen has inhibitory effect on neutrophil apoptosis and neutrophils may play an important role in allergic inflammatory process.

3411 Late-breaking abstract: House dust mite triggering of Dectin-2 is critical for the initiation of allergic airway inflammation

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Introduction: How the immune system senses aeroallergens and triggers an aberrant inflammation is poorly understood. Dectin-2 is a house dust mite (HDM)-sensing pattern recognition receptor, and its expression on dendritic cells is required for the Th2-skewed adaptive response to HDM.

Objective: To define the role of Dectin-2 in HDM-induced allergic airway inflammation and its expression in biopsies from asthmatic patients.

Results: In a 3 week mouse model of repeated intranasal HDM challenge, pro-inflammatory cytokine production by dendritic cells was detected within the first 24 hours of challenge. This was associated with recruiting lymphocytes and eosinophils were elevated in the airways of allergic GF mice. The resulting cellular infiltrate and cytokine production were measured. (SPF) or recolonized mice by sensitization and challenge with ovalbumin (OVA).

Methods: To define the mechanism by which Dectin-2 triggers HDM-induced inflammation, we conducted in vivo experiments using cultured alveolar macrophages. These indicated that Dectin-2 was necessary for the induction of cysketyl leukotrienes, as reported for dendritic cells, but not chemokines or cytokines. Furthermore, we demonstrated in our single challenge model that leucine, an inhibitor of leukotriene production, produced a similar effect as Dectin-2 blockade. Finally we found a marked increase in the number of Dectin-2 positive cells in bronchial biopsies from asthmatic subjects when compared to normal controls.

Conclusions: Alveolar macrophage sensing of HDM by Dectin-2 elicits the production of cysketyl leukotrienes, and this axis is key for the initiation of allergic airway inflammation. Dectin-2 is associated with asthma.

3412 Late-breaking abstract: Dyserregulation of allergic airway inflammation in the absence of microbial colonization

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Rationale: The incidence of allergic disorders is increasing in developed countries and has been associated with reduced exposure to microbes and alterations in the commensal bacterial flora.

Objectives: To ascertain the relevance of commensal bacteria upon the development of an allergic response, we utilized a model of allergic airway inflammation in germ-free (GF) mice that lack any exposure to pathogenic or non-pathogenic microorganisms.

Methods: Allergic airway inflammation was induced in GF specific pathogen free (SPF) or reconstituted mice by sensitization and challenge with ovalbumin (OVA). The resulting cellular infiltrate and cytokine production were measured.

Measurements and main results: Our results show that the total number of infiltrating lymphocytes and eosinophils were elevated in the airways of allergic GF mice as compared to control SPF mice, and that this increase could be reversed by re-colonization of GF mice with the complex commensal flora of SPF mice. Exaggerated airway eosinophilia correlated with increased local production of Th2 associated cytokines, elevated IgE production and an altered number and phenotype of conventional dendritic cells (cDC). Regulatory T cell populations and regulatory cytokine levels were unaltered but GF mice exhibited an increased number of basophils and decreased numbers of alveolar macrophages (AM) and plasmacytoid dendritic cells (pDC).

3413 Late-breaking abstract: Relationship with hemoglobin A1c and exacerbations of COPD: A preliminary study

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Background and objective: Hyperglycaemia during hospital admission is associated with poor outcomes in patients admitted with acute myocardial infarction, stroke and pneumonia. Systemic inflammation may represent a possible cause of glycolytic metabolic disorder. We studied that association Hemoglobin A1c with an increased risk of acute exacerbation of COPD (AECOPD).

Methods: Patients with COPD were prospectively enrolled and followed between 2010 and 2011. Medical records, HbA1c, fasting glucose and metabolic markers were assessed in 29 patients.

Results: A total of 29 patients (mean age of 78.2 years) were recruited, 11 with AECOPD and 18 without. Clinical data were collected from the patients. HbA1c levels of AECOPD patients were significantly higher on entry point compared with other patients (5.783±0.2638; 4.983±0.1778, respectively p=0.0361). Moreover, there was a trend for increased length of stay and frequency of admissions in patients with higher levels of HbA1c. (4.5%<HbA1c<5%; 5%<HbA1c<5.5%; 5.5%<HbA1c<6%; HbA1c<6%, 15days (0.9/year (y)); 26days (1/y); 23days (1.3y); 30days (2.3y), respectively).

Conclusion: Previous study revealed that comorbid diabetes prolongs length of stay and increases risk of death in patients with AECOPD. However, less evidence exists for relationship of HbA1c with AECOPD. For the first time our study demonstrates that HbA1c is a prognostic factor associated with AECOPD. Taken together with a previous study that revealed a similar trend, our study suggests that further studies are now required to elucidate the reasons for these poorer outcomes, in particular whether glycaemic control or input control is responsible, as these are potentially modifiable factors.

3414 Late-breaking abstract: Further studies on the mechanism of action of doxofylline

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Xanthines such as theophylline have been used in the treatment of lung diseases since the early 1900’s, but have a major drawback of a very narrow therapeutic window and many drug-drug interactions. This means that regular plasma levels often have to be obtained and can make the use of theophylline problematic. With the increasing availability of other classes of drugs for the treatment of respira-toary diseases, this has limited the use of xanthines, despite their clean clinical benefit in the treatment of patients with asthma and COPD. Doxofylline is a xanthine molecule having both bronchodilator and anti-inflammatory activity, with a lower improved therapeutic window over conventional xanthines such as theophylline. However, the mechanistic basis of this improved therapeutic window is not understood. The present study has investigated the ability of doxofylline to inhibit human recombinant PDE and HDAC enzymes, and find to adenose receptor assays in vivo in comparison with theophylline. We have found that adenose receptor binding that was not shared by doxofylline. Our results suggest that doxofylline may have a wider therapeutic window than theophylline due to a lack of adenose receptor antagonism. Neither drug had any significant inhibitory effect on HDAC enzymes over a wide range.

Additionally, in contrast to doxofylline, theophylline showed a significant effect on PDE3. It has been suggested that the ability of theophylline to inhibit HDAC enzymes may contribute to the unwanted cardiovascular effects observed at higher serum concentrations. The lack of effect of doxofylline on PDE3 may also help explain its improved tolerability profile on the cardiovascular system.
Flow-volume loops in central airway obstruction
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Introduction: Central airway obstruction (CAO) leads to significant morbidity and mortality. In the last 40 years flow-volume loops (FVL) have been used as a noninvasive method to evaluate this condition although bronchoscopy is the gold standard. Few studies were made to verify the sensitivity and specificity of FVL in detecting CAO, or to investigate the morphological and quantitative changes of the curve in relation to location, type and degree of obstruction.

Methods: Patients with an indication to perform bronchoscopy were selected consecutively. Bronchoscopy and FVL were carried out with a maximum interval of 7 days. Four experts, blinded to the quantitative data, were used to assess the morphology of FVL (suggestive or non-suggestive of CAO) and an independent element established the quantitative and morphological criteria (intra, extrathoracic variables and fixed).

Results: 82 patients were studied, 36 (44%) with CAO. The sensitivities and specificities in detecting CAO were, respectively: 91.3% and 88.9% for the quantitative criteria of FVL; 93.5% and 30.6% concerning the morphological criteria; 95.7% and 86.1% if there was an aggregation of quantitative and morphological criteria. In patients with CAO the most common quantitative criteria were FEF50/FIF50 (83%) and FEV1/PEF (86%). They correlated with localization, degree and type of obstruction.

Conclusions: The morphology of the FVL has a good sensitivity but low specificity in detecting CAO. Quantitative criteria of the FVL have a high sensitivity and specificity. In clinical practice one should always use an aggregation between the quantitative and morphological criteria.

Survival analysis can help determine which TLco prediction equations to use for patient data
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Choosing which prediction equation to use for lung function data can be a problematic. In Europe the ECCS equations are commonly used but more recent ones are available and may be more applicable. To help decide which TLco prediction equations would be best for our data we extracted the earliest results for subjects from our lung function database who had a full set of all tests and determined their survival up to 29/12/2009. We calculated TLco results as standardised residuals (SR) using equations from ECCS (1993), RO Crapo (1981), A Miller (1983) and CM Roberts (1991) and used deciles of these results and of age and included sex to predict survival. There were full data for 5626 subjects (48% women) with mean (SD) age 59.3 yrs (14.7), mean survival 4.4 yrs (SD 2.6, range 0 to 24) with 2049 deaths. Using the ECCS equations the mean (range) of SR values for FEV1 was -1.6 (-7.3 to +3.4), for FVC was -0.8 (-6.3 to +3.6) and for TLco was -1.5 (-6.5 to +6.2). The best Cox survival prediction model (highest Chi² value) was with the Miller equations as shown in the table of hazard ratios (95% CI) for death associated with oldest age decile, worst TLco decile and sex.

We conclude that for our UK data the Miller equations from the USA for TLco are the best related to subsequent survival and so should be considered for determining if results are abnormal.

418 Evaluating the FVC-reference equation for female
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Introduction: At World Spirometry Day we measured lungfunction in hospital staff (n=99, m=40, l=59) in Amersfoort, the Netherlands. We were struck by the high scores in FVC in the female group. In the group of healthy, never-smoking female (n=36) (Ages 18-64) we discovered that mean FVC was 114% pred. Other studies about this subject show that reference values for male have not enough correction for aging, but are quite correct for height.

Aim: Understand which element of the reference-equation for female doesn’t fit properly, and search for alternatives.

Methods: First we analysed the ECCS reference equation for FVC in female: 4.3H - 0.026A - 2.89 (H=height in m, A=age in y) (ERD 1993.) Then we made a statistical analysis for FVC% pred. (y) and age (x) and FEV1% pred. (y) and height (x). Analysis: The statistics show that female from 18-44 yrs. have a lower FVC% pred. (n=16, mean FVC = 106.96%) than female from 45-64 yrs. (n=18, mean=120% pred.) We see that female between ages 45-64 have a moderate height (160-170cm) but the highest scores. There is a linear relation between age and FVC% pred.<p>0.055 Concerning height: Only in female with real high FVC% pred. (=>120%) we see a relation between height and FVC% pred.(p<.009) Analyzing the equation we discovered that for tiny female a volume is subtracted for aging as there is in taller female and even in male.

Conclusion/Discussion: Aging of the lung should be related to the volume of that specific lung. We have high expectations of the new reference equations introduced by taskforce of Global Lung Initiative. In the clinical setting there’s a risk of underestimating restrictive patterns in tiny elderly female when applying the ECCS reference equations.

419 How many forced spirometry efforts are useful in moderate to severe COPD patients?
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The 2005 ERS/ATS guidelines on spirometry have established a maximum number of 8 efforts in a forced spirometry test. The aim of this work was to evaluate which effort produces the highest value for FEV1, FVC, PEF, and FEV1/VC in COPD patients.

We used the data collected in a phase II multicenter clinical trial (TESRA, sponsored by F. Hoffmann – La Roche Ltd) to evaluate the parameter trend in multiple efforts of forced spirometry in moderate to severe COPD patients with emphysema. All of the 73 test centers in 12 countries were equipped with the identical device (MasterScreen PFT, CareFusion, Hoechberg, Germany). The data was collected electronically and reviewed for quality and acceptability by a central overreader. 6 075 test sessions (screening and treatment) with 20 482 valid efforts from 1 183 patients were evaluated. On average 3.4 valid efforts were performed per test.

The per effort parameter values were expressed as a percentage of the highest (best) value per test session. The median values per effort number across all tests ranged from 95% to 99% for FEV1, FVC and FEV1/VC. The highest median values were achieved in efforts 3 and 4. For PEF the median values ranged from 92% to 98%, with the highest values in the first effort. FEV1 and PEF showed a marked decrease in late efforts.

The drop in the PEF and FEV1 values illustrates the increasing fatigue of the COPD patients. The relative FEV1 values were lower than the relative FVC values, indicating that it is more complicated for patients to sustain good FEV1 values. Unless errors in the technique are observed, it is unlikely to achieve higher values after the 5th effort.

420 Vital capacity after lung transplantation
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Introduction: The size of the Vital Capacity (VC) is determined by powers between thorax and lung. After lung transplantation it will take some time before an equilibrium is settled between thorax mobility and lung compliance. VC therefore increases over time until a maximum is reached (VCmax). Aims: The aim of our study was to investigate how long it takes to reach VCmax. Also we wanted to find out if age at transplantation, pre-transplantation value of FEV1/VC, single or double lung transplantation and gender influenced the duration to reach VCmax.
3421
Recurrent for referral for pulmonary function testing: An audit of four Australian adult lung function laboratories
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Pulmonary function (PF) testing provides a cornerstone for diagnosis and management of most respiratory conditions. Accurate interpretation of test results is an important component of the final report. As part of developing a structured approach to interpretation of PF results we wished to characterise primary reasons for referral testing in a range of PF laboratories.

Methods: Three public university-affiliated PF labs and one private lab using similar PF databases participated. Reasons for performance of PF tests were extracted from the databases and collated for analysis. Over 5,000 consecutive tests were evaluated from each lab.

Results: The main reason for referral was found in 83% of 24,602 test results and categorised. The major categories were follow-up of known respiratory disease (53% of 20,308 tests), investigation of specific symptoms (18%), and assessment of lung function (13%). The absence of clinical complications and the maintenance of stable lung function over a 5-y period post-BT in patients with severe refractory asthma suggest long-term safety of the procedure out to 5 y. There were no incidences of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 y.

Conclusions: The absence of clinical complications and the maintenance of stable lung function over a 5-y period post-BT in patients with severe refractory asthma suggest long-term safety of the procedure out to 5 y.

3422
Safety of bronchial thermoplasty out to 5 years in patients with severe refractory asthma: Research in severe asthma (RISA) trial
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Efficacy of high-dose leukocytapheresis using extracorporeal circulation through a large leukocyte-removal filter column in patients with refractory asthma
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Leukocytapheresis (LCAP) as well as granulocyte and monocyte adsorptive apheresis (GMA) using extracorporeal circulation through the column has been used to treat inflammatory bowel disease and rheumatoid arthritis in Japan. We previously reported that GMA improved the peak expiratory flow rate (PEFR) in patients with severe asthma. To evaluate the efficacy of high-dose leukocytapheresis (pulse LCAP) using a large leukocyte-removal filter column (Cellsorba® CS-180S, Asahikasei Kuraray Medical, Tokyo, Japan) in patients with refractory asthma, we conducted a clinical trial. Pulse LCAP was performed 2 sessions at 1-week interval and 5 L of blood was filtered per session. The average PEFR during the 4 weeks just after the second LCAP in each patient was compared with that during the 4 weeks just before the first LCAP as a primary end point. The sum total of asthma control test (ACT) score at 4 weeks after the second LCAP was compared with that just before the first LCAP as a secondary end point. We evaluated the change of the fraction of exhaled nitric oxide (FENO) in each patient before and after pulse LCAP as a biomarker of eosinophilic airway inflammation. Five patients fulfilled the ATS criteria for refractory asthma participated in this trial up to now. The morning PEFR and the ACT score were increased in all patients. Although FENO was abnormally increased in four patients in spite of the standard therapy, it was decreased after pulse LCAP. Pulse LCAP might serve as a non-pharmacological strategy to induce clinical improvement in patients with refractory asthma through its unique anti-inflammatory effects.

382. New treatments for airway disease

3424
The effect of GSK2190915, a 5-lipoxygenase activating protein inhibitor, on the allergic induced asthmatic response
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Objective: To assess the effect of GSK2190915 on the allergic-induced asthmatic response.

Methods: 19 eligible patients with mild asthma were enrolled and completed this 4-centre, double-blind, 2-way crossover study. They took 100 mg GSK2190915 and placebo orally once daily for 5 days, in randomised order. On Day 3 they had an inhaled allergen challenge and on Days 4 and 6 they had induced sputum collection.

Results: GSK2190915 attenuated the early (0-2 hours) and late (4-10 hours) asthmatic response to inhaled allergen compared to placebo. Following GSK2190915, the mean% attenuation of the placebo response to inhaled allergen for the minimum and weighted mean FEV1 (0-2 hours) was 33.3% and 62.6%, respectively, and the
mean% attenuation of the placebo response to inhaled allergen for the minimum and weighted mean FEV1 (4-10 hours) was 15.8% and 22.7%, respectively. There was a significant attenuation of the allergen induced increase in spurt percent eosinophil count on Day 4 following GSK2190913 compared to placebo; the treatment difference (95% CI) was -9.95% (±18.13, -1.77). There was a >-90% reduction in spurt LTBB4 on Days 4 and 6 following treatment with GSK2190913 compared to placebo. Median spurt LTBB4 (pg/mL) was 524 and 837 on Days 4 and 6 following placebo, and 31 and 18 on Days 4 and 6 following GSK2190915. Safety and tolerability were good.

Conclusion: GSK2190915 shows potential as a treatment for asthma. ClinicalTrials.gov identifier NCT07748306

3425
Phase II randomized, double-blind, placebo-controlled study of tralokinumab, an anti-IL-13 monoclonal antibody, in moderate to severe asthma
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Background: IL-13 is hypothesized to be a critical mediator in the development and maintenance of the asthma phenotype.
Aim: To assess clinical activity and safety profile of tralokinumab (TK; CAT-354), a human IgG4 monoclonal antibody that specifically neutralizes IL-13.
Methods: After a 2-week run-in, 194 subjects (52% atopic) with uncontrolled moderate-severe asthma despite standard controller treatment (ACQ ≥ 6 ± 3 exacerbation in last year) received SC TK (150 mg, 300, or 600 mg) or placebo (PBO) every other week (7 doses) in addition to continued controller treatment. The primary endpoint was change in ACQ-6 score at week 13 (combined TK groups vs PBO).
Results: At baseline mean (SD) age was 47 yr (10.8), ACQ-6 score was 2.7 (0.6), and proportion of exacerbation-free subjects was 28%. At Wk 24, NV A237 numerically reduced the rate of moderate/severe exacerbations compared with NV A237 vs PBO (0.43 vs 0.59/yr; rate ratio [RR] 0.72; p=0.071).
Conclusion: In patients with moderate-to-severe COPD, compared with placebo, NV A237 50 μg OD or placebo (PBO) via a low-resistance single-dose dry powder inhaler (Concept1 device) for 26 wks. In addition to bronchodilatation (primary efficacy endpoint was trough FEV1, at 12 wks), the effect on COPD exacerbations and related hospitalizations was assessed using a Cox regression model.

3426
Efficacy of an anti-IL13 monoclonal antibody, lebrikizumab, in adults with inadequately controlled asthma is enhanced in those with high periostin levels
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Introduction: COPD exacerbations, especially those leading to hospitalization, have a significant impact on patients’ quality of life and long-term prognosis. We examined the influence of the non-daily (QD) long-acting muscarinic antagonist NVA237 (glycopyrronium bromide) on exacerbations of COPD.
Methods: Patients with moderate-to-severe COPD were randomized (1:1) to double-blind NVA237 50 μg OD or placebo (PBO) via a low-resistance single-dose dry powder inhaler (Concept1 device) for 26 wks. In addition to bronchodilatation (primary efficacy endpoint was trough FEV1, at 12 wks), the effect on COPD exacerbations and related hospitalizations was assessed using a Cox regression model.
Results: 822 patients were randomized: 80.5% completed. Mean age was 63.9 yrs, mean post-bronchodilator FEV1, 54.6% predicted (FEV1/FVC 0.5). Compared with PBO, NVA237 significantly prolonged the time to first moderate/severe COPD exacerbation (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.50-0.93) and the time to first severe COPD exacerbation leading to hospitalization (HR 0.35, 95% CI 0.14–0.85; p=0.022). NVA237 also significantly reduced the percentage of hospitalizations due to COPD exacerbation (odds ratio [OR] 0.34; 95% CI: 0.19-0.62; p<0.001).
Conclusion: In patients with moderate-to-severe COPD, compared with placebo, NVA237 50 μg once daily significantly prolonged the time to first moderate/severe COPD exacerbation and reduced the percentage of hospitalizations due to COPD exacerbation.

3428
Pleiotropic effects of add-on atorvastatin therapy during the treatment of COPD patients
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The potential role of statins in treating COPD is controversial and it is unclear what anatomic COPD lesions patients affect. We have performed a prospective study to compare Atorvastatin 40mg once daily for three months in thirteen COPD patients (8 ex-smokers (ExSm) and 5 current smokers (CurrSm)). Transbronchial lung biopsy was carried out at baseline and after treatment. Twelve subjects, 11 males and 1 female, mean age 64.58 (min 56, max 78) completed the study and 48 paired biopsies were available for analysis. Lung function and cardiopulmonary exercise tests, SGRQ, 6MW test, and Holter EKG monitoring were performed, and serum lipids and hs-CRP were measured. Lung biopsy specimens were processed for histology, immunohistochemistry with anti CD45, CD11b, P-selectin, ETAR, and ET-1 antibodies. 8-iso-prostanate levels and differential cell count were measured in induced sputum.

Results: Symptoms significantly improved. There was no significant change in FEVI, but IC improved (In ExSm: from 55.54% predicted (%) to 64.4-0.01, In ExSm: from 81.93% to 89.5%, p=0.05, before and after therapy, respectively). TGV decreased from 119.92% to 113.69%; p<0.05, and RV/TC improved in ExSm: from 44.01% to 40.07%, p=0.05 before and after therapy, respectively. In lung biopsy there were significant decreases in inflammatory cells numbers, CD4+ cells decreased in CurrSm from 30.40% to 20.95% and in ExSm, from 61.40% to 18.94%, p<0.05 before and after treatment, respectively. The expression of CD11b, P-selectin, ETAR, and ET-1 were also decreased after therapy. These data indicate that the use of atorvastatin may have potential beneficial effects in COPD patients through an anti-inflammatory mechanism.

6088s
3429 Beta-blockers in chronic obstructive pulmonary disease – A retrospective cohort study
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Background: Beta-blockers are avoided in COPD patients.
Objectives: We examined the use of beta-blockers and their relationship with established stepwise pharmacological managements for COPD assessing their effects on mortality, exacerbations and pulmonary function.
Methods: Retrospective cohort study using a disease specific database of COPD patients (TARDIS) linked to NHS databases providing information on hospital admissions, drug prescriptions and death. Adjusted Hazard ratios were calculated through Cox Proportional Hazard Regression after correction for covariates, including history of overt cardiovascular disease.
Results: 5,977 patients, mean follow up 4.35 years, mean age 69.1 years, 88% of beta-blockers were cardio selective. There was a 22% overall reduction in all-cause mortality with beta-blocker use. Furthermore there were additive benefits of beta-blockers on all-cause mortality at all COPD treatment steps. Compared to controls the adjusted hazard ratio (95%CI) for all-cause mortality was 0.28 (95%CI 0.21 to 0.39) for inhaled corticosteroid + long acting beta-agonist + long acting anti-muscarinic + beta-blocker versus 0.43 (95%CI 0.38 to 0.48) without beta-blocker. There were similar trends showing additive benefits of beta-blockers in reducing oral steroid use and respiratory hospital admissions. Beta-blockers had no deleterious impact on FEV1 or FVC at all treatment steps when given with a LABA or LAMA.
Conclusions: Our study suggests beta-blockers may reduce mortality and exacerbations when added to established inhaled therapy for COPD, independently of overt cardiovascular disease and cardiac medications, and without adverse effects on pulmonary function.

383. Pathobiology of experimental pulmonary hypertension

3430 Late-breaking abstract: Intracellular mechanisms behind the effect of C-reactive protein on proximal vascular cells of CTEPH patients
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Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with vascular remodeling and inflammation. Our latest results showed that C-reactive protein (CRP) could contribute to vascular remodeling and endothelial dysfunction in pulmonary vascular cells of CTEPH patients. We aimed to investigate the intracellular mechanisms responsible for the effect of CRP on CTEPH pulmonary vascular cells. Pulmonary proximal arterial endothelial (EC) and smooth muscle cells (SMC) were isolated from patients with CTEPH. After stimulation with CRP, total RNA was extracted from CTEPH-EC and CTEPH-SMC and first stand cDNA was generated. A RT2 profiler PCR Array (SABioscience) was used to evaluate the expression of 84 key genes related to NFκB-mediated signal transduction. Different genes from the NFκB pathway were up- or downregulated in CRP-stimulated CTEPH-EC and CTEPH-SMC. In CRP-stimulated EC isolated from 5 different CTEPH patients, the serotonin receptor 1B was significantly downregulated (p=0.012) and the serotonin receptor 1D was significantly upregulated (p=0.012) compared to not stimulated CTEPH-EC. CRP significantly downregulated the toll-like receptor 4 (p=0.032) and inhibitor of kappa B light polypeptide (p=0.025) in CTEPH-EC. In CRP-stimulated SMC isolated from 4 different CTEPH patients, mucosa associated lymphoid tissue 1 (p=0.038) and B-cell lymphoma 10 (p=0.012) were significantly upregulated. These results suggest an involvement of the NFκB pathway in mediating the effects of CRP on vascular cells of CTEPH patients.

3431 Human pulmonary arterial hypertension bone marrow-derived CD133+ myeloid progenitors induce vascular remodeling in immunodeficient mice
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Severe remodeling of the pulmonary artery is the hallmark of idiopathic pulmonary artery hypertension (IPAH). Myeloid CD133+ proangiogenic progenitors, which oversee vascular homeostasis, are increased in IPAH. We hypothesized that IPAH CD133+ cells are derived from a predominantly myeloid bone marrow (BM) stem cell that promote the pathologic vascular pulmonary remodeling. CD133+ cells sorted from IPAH, unaffected family members or healthy control BM aspirates, were engrafted into immunodeficient mice and analyses were performed after 7 weeks or if mice became moribund. Recipients of PAH or unaffected family member CD133+ cells had higher engraftment and myeloid differentiation as indicated by higher human CD45+ and CD33+ cells. Mice engrafted with PAH CD133+ cells had higher plasma von Willebrand Factor (vWF) as compared to control mice, indicating endothelial activation, and demonstrated higher morbidity and mortality. Histological examination of organs revealed cardiac and pulmonary remodeling in PAH recipients, but no remodeling in the control group. Tissue remodeling included in situ thrombi, muscularization of pulmonary arteries, right ventricular hypertrophy, infarction and ischemia. PAH recipients had a 2-fold increased microvessel density in lungs but not in heart or liver. Lung microvesSEL density correlated to circulating human progenitors in the mouse circulation. Collectively, the data suggest that the development of PAH precedes CD133+ proangiogenic myeloid progenitor cell proliferation that contributes to the progression and/or pathogenesis of PAH, possibly through endothelial cell injury/plaque activation.

In the failing RV, IL-1α, IL-1β and TNF-α expression were locally increased along with increased circulating levels of TNF-α. RV capillary densities were similar between the 2 groups, while gene expressions of VEGF and angiotensin-2 were decreased in the failing RV tissue. Prolonged left-to-right shunting in pigs does not further aggravate PAH, but is a cause of RV failure, which appears related to an activation of apoptosis, hypertrophy and inflammation.

3433 Expression and role of the nerve growth factor NGF in pulmonary hypertension
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Introduction: Our previous studies showed an increased NGF expression in animal models of pulmonary hypertension (PH) and suggested a role for NGF in various aspects of this disease. We have studied here expression of NGF and its receptors in human PH, and investigated whether administering anti-NGF blocking antibodies in vivo prevented some pathological aspects in a rat PH model.
Methods: NGF and inflammatory cytokine secretion was assessed by ELISA in human pulmonary arteries (PA) from controls or from patients with secondary PH. Expression of NGF receptors (TrkA and p75NTR) was assessed by Western blotting. In the rat, PH was induced by monocrotaline (MCT, 71, 60mg/kg ip), with or without administration of anti-NGF blocking antibodies (J0, J2, J7, 10μg/kg ip). Pulmonary arterial pressure (Pap) and Fulton index were assessed at J28. PA medial wall thickness was evaluated on lung sections after hematoxylin and eosin staining. PA reactivity to phenylephrine or prostaglandin E2 (PGE2a) was assessed ex vivo.
Results: Significant increase in expression of NGF and its receptors was observed in PA from patients with secondary PH compared to controls. In the MCT-treated
rat, anti-NGF blocking antibodies significantly reduced Pap, Fulton index, cytokine secretion, PA medial wall thickness, and totally prevented PA hyperreactivity to phenylephrine or PGF2α.

**Conclusion:** Our data show that expression of NGF and its receptors are increased in human PH. Moreover, administration of anti-NGF blocking antibodies in the rat in vivo partially prevented PH by modulating PA hyperreactivity, inflammation and remodeling. These results therefore confirm that targeting NGF may be of therapeutic interest in this disease.

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**Inflammatory processes in load-induced right ventricular failure**

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**Background:** Transient increase in pulmonary arterial (PA) pressure has been shown to induce a persistent right ventricular (RV) failure characterized by a RV-arterial decoupling, associated to activation of apoptotic pathways and local overexpression of TNF-alpha (Dewachter et al. Crit Care Med 2010; 38: 1405-13).

**Objectives:** We hypothesized therefore that inflammatory cytokines might contribute to the development of persistent RV failure in this “pulmonary hypertension crisis” model.

**Methods:** Sixteen dogs were randomized to a 90-min PA constriction- or to a SHAM-operation, followed 30 minutes later by hemodynamic measurements including effective pulmonary arterial elastance ( Ea) to estimate RV afterload and RV end-systolic elastance (Ees) to estimate RV contractility determined by the single beat method (Brimioulle et al. Am J Physiol 2003; 284: H1625-30), but also blood sampling. After sacrifice of the animals, the RV free wall was sampled for gene and protein expressions of interleukin (IL)-1 beta, 6 and 10.

**Results:** The transient increase in PA pressure persistently increased Ea, and decreased Ees, Esv/Ea and cardiac output, indicating RV failure with altered RV-arterial coupling. As compared to the SHAM group, 90-min PA constriction increased RV relative gene and protein expressions of IL-1 beta and IL-6, and decreased RV relative gene and protein expressions of IL-10, an anti-inflammatory cytokine. The pro-inflammatory IL-6/IL-10 ratio was increased in the RV and in the serum in the PA constriction- compared to the SHAM- group.

**Conclusions:** Acute afterload-induced persistent RV failure appears to be related to local and systemic activation of inflammation.

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**Right lung ischemia induces development of contra-lateral pulmonary vasculopathy**

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**Chronic thromboembolic pulmonary hypertension is due to mechanical obstruction by unresolved clots and vasculopathy in the non obstructed vascular lung regions. We tested whether flow induced vascular lesions or endocrine factors released by the ischemic lung account for development of vasculopathy in non obstructed regions.**

3 groups of 5 piglets were studied 5 weeks after right pulmonary artery (PA) ligation (PAL group), right pneumonectomy (RP group) or right PA dissection (Sham group). We measured pulmonary vascular resistance, pulmonary arterial vasoreactivity and morphometry, and quantified gene expression of factors involved in vascular smooth muscle cell proliferation IGF, PDGF, VEGF and endothelin-dependent vasoreactivity pathways ET-1, ETA, ETB and eNOS. As compared to RP, PAL animals developed pulmonary vasculopathy in the left lung as assessed by increase in pulmonary vascular resistances (p=0.0016), medial hypertrophy of the distal PA (p=0.0001), decreases in both maximal relaxation to acetylcholine (p=0.013) and eNOS gene expression (p=0.041). Left lung IGF (p=0.034), PDGF (p=0.0066) and VEGF (0.0105) gene expressions increased in the PAL group when compared to both RP and Sham. ETAa and ETBb expression was downregulated in both RP (p=0.048 and p=0.039) and PAL (p=0.033 and p=0.028) groups.

**Pulmonary vasculopathy is absent in the remaining lung 5 weeks after pneumonectomy and developed in the non obstructed pulmonary territories 5 weeks after right PA ligation suggesting that factors released by the ischemic lung induced vascular remodelling in the contra-lateral lung. This endothcne regulation might implicate release of factors involved in vascular smooth muscle cell proliferation.**

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**p53-dependent, replicative cell senescence suppresses chronic hypoxia-Induced pulmonary hypertension in mice**

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**Introduction:** Excessive telomere shortening limits both cell proliferation and tissue regenerative capacity by inducing senescence, a permanent growth arrest mediated by the p53 pathway. The purpose of this study was to evaluate the susceptibility of mice with defective telomerase (Terc−/−) to develop hypoxia-associated pulmonary hypertension (PH).

**Methods:** Terc−/−, p53−/− Terc−/−, and wild-type (WT) mice at 12 weeks of age were randomly divided into two groups, one of which was maintained in room air (normoxia) and the other exposed to normobaric hypoxia (15% oxygen, 95% nitrogen) for 3 weeks. We evaluated pulmonary hemodynamics, vascular remodeling, and the p53-mediated response in the lung.

**Results:** The Terc−/− mice were efficiently protected against chronic hypoxia-induced PH as compared to WT mice. Interestingly, Terc−/− mice exhibited marked increase in p53 protein levels under normoxia and lacked all signs of tissue remodeling associated to vascular cell proliferation seen in WT mice upon hypoxia treatment. Remarkably, p53 heterozygous Terc+− mice were fully susceptible to hypoxia-induced PH and developed all cell proliferation-related histopathological manifestations.

**Conclusions:** Taken together, these results show that a telomere-mediated, p53-dependent, senescence in vascular tissues confers a strong protective effect on chronic hypoxia-induced PH in mice.

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**Right ventricular oxygen supply and diffusion in human and experimental pulmonary hypertension**

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**Introduction:** In pulmonary hypertension (PH), right ventricular (RV) oxygen supply has to increase to meet the higher oxygen consumption due to the high RV output. To investigate how the RV adapts to meet these requirements, we studied the oxygen supply and intracellular diffusion in terms of capitalization and myoglobin content in patients with PH. In addition, we compared healthy rats to a rat model with stable PH (preserved cardiac output) and progressive PH (RV failure) to answer the question whether adaptations in oxygen handling are characteristic for the failing RV or develop during progression of the disease.

**Methods:** RV tissue was collected at autopsy of 10 diseased PH patients and 10 control patients who died from a left ventricular myocardial infarction. In rats, stable PH and progressive PH were induced by monocrotaline 40 and 60 mg/kg, respectively. RV cardiomyocyte cell size, capillary density and myoglobin content were determined.

**Results:** RV cardiomyocyte cell size is strongly increased in PH patients compared to controls (PH: 823±125 vs con: 553±67 μm², p<0.001), while capillary density was decreased (PH: 557±110 vs con: 1119±195 capillaries/mm², p<0.001). RV myoglobin content was significantly reduced (PH: 0.56±0.18 vs con: 1.0±0.34 a.u., p<0.05) thus showing reduced intracellular oxygen diffusion. Similar results were found in the failing RV of progressive PH rats. Furthermore, stable PH rats showed an intermediate state from healthy to failing RV.

**Conclusion:** Oxygen supply to and diffusion within the cardiomyocytes is reduced in both failing human and rat RV. This is characteristic for the failing RV since stable PH rats maintained supply and diffusion.

384. Outdoor air pollution studies

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**Late-breaking abstract: Do emissions from animal farms affect the airways of neighboring residents?**

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**Concerns about public health risks of intensive animal production in The Netherlands continue to rise, in particular related to outbreaks of infectious diseases such as Q-fever. An increased risk of asthma among neighboring residents is a specific concern raised by general practitioners (GPs) in areas with high animal densities. The aim was to study respiratory health effects among individuals living in the vicinity of animal farms.**

**Associations between farm exposure variables and respiratory diseases were analyzed using a Geographic Information System. Electronic medical record data for the year 2009 of all patients of 27 GPs in a region with a high density of animal farms were used. Density of animal farms around the home address was calculated using a Geographic Information System. Associations between farm exposure variables and respiratory diseases were analyzed using a Geographic Information System.**

**Results:** A Q-fever outbreak occurred in 22.406 children (0-17) vs 70.142 adults (18-70 y), adjusting for age, sex, and household income. During the study period, a Q-fever outbreak occurred in...
Late-breaking abstract: Pneumonia hospitalizations and long-term exposure to air pollution

Aim: To investigate the effect of long-term exposure to traffic-related air pollution (up to 38 years) in Copenhagen and Aarhus on hospital admissions for pneumonia.

Methods: We followed 57,053 participants of Danish Cancer, Diet, and Health cohort, aged 50-65 years at baseline (1993-1997) in Danish hospital discharge register for first hospital admission for pneumonia between baseline and 2010. The annual nitrogen dioxide (NO\textsubscript{2}) levels were estimated at residential address since 1971 as a proxy of exposure to traffic-related air pollution. We modelled the association between mean NO\textsubscript{2} levels and hospitalizations for pneumonia using Cox regression.

Results: During 12.7 years’ mean follow-up, 3,024 (5.7%) out of 53,239 eligible people were admitted to hospital for pneumonia. Mean NO\textsubscript{2} levels were significantly higher as a risk for first-ever pneumonia hospitalization in the full cohort (hazard ratio and 95% confidence interval per double mean exposure: 1.25; 1.13-1.35); with similar effect for first-ever pneumonia admission in 46,462 people with a history of asthma hospitalization (1.41; 1.33-1.49). Enhanced associations were observed in 485 people who had a history of pneumonia hospitalizations (1.45; 0.85-2.47).

Conclusions: Living in areas with high traffic-related air pollution increases the risk of hospitalization for pneumonia.

Impact of climate change on ozone induced mortality in Europe

Background: Ozone is a highly oxidative pollutant, associated with respiratory morbidity and mortality. All else being equal, ground-level ozone will increase as temperatures increase with climate change.

Aim: As a part of the Climate-TRAP project we used emission scenarios, models and epidemiological data to assess ozone-related health impacts under a changing climate.

Methods: European ozone concentrations were modelled at a grid size of 50x50 km using MATCH-RCRA. Projections from two climate models, ECHAM4 and HADLEY, were used, assuming greenhouse gas emission scenarios A2 and A1B. Four periods were compared: the baseline period was defined as 1961–1990, the current situation as 1990–2009, nearer future as 2021–2050 and further future as 2041–2060. The impact on mortality (short-term effect) was calculated for exposures above a daily maximum 8-hour concentrations of 70 \mu g/m\textsuperscript{3}. We use a European-wide exposure-response function with country-specific baseline mortality.

Results: Comparing the current situation with the baseline period, the largest increase in ozone-associated mortality due to climate change (~4%) occurred in Belgium, Ireland, Netherlands and UK. Comparing the baseline period and the further future, the increase is projected to be biggest in Belgium, France, Spain and Portugal (10–14%) and the effect will be stronger for the A2 scenario. However, in Nordic and Baltic countries there will be a decrease in ozone-related mortality of the same magnitude.

Discussion: The current study suggests that projected effects of climate change on ozone levels could differentially influence mortality and morbidity across Europe.

Long-term exposure to air pollution and asthma hospitalizations in elderly adults: A cohort study

**Background:** Exposure to air pollution in early life contributes to the burden of childhood asthma, but it is not clear whether lifetime exposure to air pollution can lead to asthma onset or progression in adulthood. We studied the effect of exposure to traffic-related air pollution over 35 years on the risk for hospitalization for asthma in elderly.

**Methods:** We followed 57,053 participants in the Danish Diet, Cancer and Health cohort, aged 50-65 years at baseline (1993-1997), for first hospital admission for asthma until 2006. Annual levels of nitrogen dioxide (NO\textsubscript{2}) were estimated at all residential addresses since 1971. We modelled the association between NO\textsubscript{2} and hospitalization for asthma using Cox regression in people with and without previous hospitalizations for asthma, and assessed effect modification by co-morbid conditions.

**Findings:** During 9.9 years’ mean follow-up, 977 of 53,695 eligible people (1.8%) were admitted to hospital for asthma: 821 (1.5%) admissions were among 53,143 people who had not and 176 (31.9%) among 552 people who had been hospitalized for asthma before baseline. NO\textsubscript{2} levels were positively associated with risk for asthma hospitalization in the full cohort (hazard ratio and 95% confidence interval per inter-quartile range, 5.8 \mu g/m\textsuperscript{3}: 1.12; 1.04-1.22), and in people without previous asthma hospitalization (1.10; 1.01-1.20), with the strongest effects for people with a history of asthma hospitalization (1.41; 1.15-1.70). Enhanced associations between NO\textsubscript{2} and admissions for asthma were observed for people with COPD (1.30; 1.07-1.52).

**Interpretation:** Air pollution is a risk factor for progression and/or onset of asthma in late adulthood.

Increased plasmatic levels of soluble HLA-G molecules are associated to short-term exposure to fine urban particulate matter

**Background:** Diesel particles have been shown to enhance allergic inflammation and immune responses. HLA-G is an atypical HLA class I molecule with immuno-modulatory properties. It is detectable in plasma in a soluble form (sHLA-G) and its production is triggered by several stimuli, including IL-10. The aim of this study is to investigate the effect of short-term exposure to traffic pollution on plasmatic sHLA-G and IL-10 levels in healthy subjects. We recruited 27 healthy non-smoking policemen exposed to traffic and 17 office workers as controls. Before and after the first weekly shift, plasmatic sHLA-G and IL-10, and lung volumes were measured in each subject. sHLA-G and IL-10 levels were analyzed by ELISA. Individual pollution exposure was estimated by airborne PM2.5 and PM10 concentrations.

**Methods:** Pre-shift sHLA-G levels were similar in both groups and increased after shift in the subjects exposed to traffic (before 10.5±0.5 vs after 12.9±4.5 ng/ml, p<0.0001), but not in controls. After shift IL-10 exhibited an opposite trend in the two groups: no changes were observed in the exposed subjects, whereas IL-10 levels decreased in office workers (before 0.7±0.5 vs after 0.5±0.4 pg/ml, p=0.03). sHLA-G cross-shift changes in exposed policemen were positively correlated with PM2.5 levels (rho=0.51, p<0.05). Lung volumes did not exhibit any change after shift in either groups.

**Conclusion:** Short-term exposure to traffic pollution affects the HLA-G system, irrespective of IL-10 levels. The results suggest that fine PM had a systemic immuno-modulatory effect that occurs without changes in lung function.

Antioxidant supplementation attenuates changes in innate immunity associated with diesel exhaust (DE) in the lung: A controlled crossover exposure study

**Background:** Oxidative stress is thought to induce negative health effects associated with exposure to DE and may result from altered innate immunity. Therefore, anti-oxidant supplementation may modify DE-related changes in phagocytosis in airways.
Methods: 12 participants (4 mild asthmatics and 8 healthy controls) completed a double-blinded, randomized, crossover, counter-balanced study of 3 exposure conditions, each separated by a 2-week washout period: (1) DE (300μg PM2.5/m3 for 2 hours with oxidant (N-acetylcycteine) 600mg 3x/day for 5 days preceding and on the day of the exposure) [“DEN”], (2) DE with placebo [“DEP”], or (3) filtered air with placebo [“FAP”]. Induced sputum was collected 6 hours after each exposure. Sputum neutrophils and macrophages were analyzed by flow cytometry for changes in innate immune response (phagocytosis). Those with PC20<8 were defined as “reactive” and those with PC20>8 as “non-reactive”.

Results: Phagocytosis in sputum macrophages was greater after DEP than after FAP (mean phagocytosis units = 22.8 and 15.8 respectively, and this difference was attenuated by DEN (mean phagocytosis units = 17.8 units). 6 subjects were methacholine-reactive at baseline; reactivity status did not modify phagocytosis.

Conclusions: DE-associated increase in phagocytosis in human airways appears mitigated by anti-oxidant supplementation (N-acetylcycteine). The suggestion that DE upregulates the innate immune response to sputum macrophages, and that this is mediated by oxidative stress, parallels novel data from our lab regarding changes in airway reactivity to methacholine in response to FAP, DEN; and DEN.

3444 Outdoor exposure to formaldehyde (CH2O) is associated with an increased risk of hospitalization for respiratory diseases in children

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Background: Children living near wood industries have an increased risk of developing respiratory diseases. Objectives: To assess if residential outdoor exposure to NO2 and CH2O was associated with the risk of hospitalization for respiratory diseases in children.

Methods: In 2006, all the children (3-14 years) living in the Viadana district (the largest wood manufacturing area in Northern Italy) were surveyed through a parental questionnaire (n=3851) and their home addresses were geocoded. Their history of hospitalization for respiratory diseases (ICD-IX: 460-519) was assessed from January 2007 to December 2009, using discharge records obtained from the local Health Unit. To assess the outdoor exposure to NO2 and CH2O, 63 passive samplers were installed in the area using a Partitioning Around Medoids (PAM) algorithm. Pollutants were monitored twice, both in winter and in summer (2007-2008).

Results: By December 2010, 3798 (98.5%) children had been traced. During the 3 years of follow-up, 121 hospital admissions, caused by respiratory diseases, occurred (annual HR = 10.8/1000/year). The HR for respiratory diseases slightly increased with increasing outdoor exposure to NO2 (μg/m3) (RR: 1.02; 95%CI: 0.95-1.10), while they were strongly associated to CH2O outdoor concentration (μg/m3) (RR: 2.41; 95%CI: 1.07-5.43).

Conclusions: Emissions from wood industries apparently have a serious impact on children’s health.

3445 Altered haemodynamic response to norepinephrine following diesel exhaust inhalation

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Introduction: Previous studies have reported an altered autonomic nervous function following exposure to particulate air pollution. Reports of increased blood pressure and reduced heart rate variability consistent with altered autonomic nervous function have been observed in chronic obstructive pulmonary disease (COPD) patients exposed to daily life pollution.

Methods: In a randomized double-blind crossover study, 14 healthy non-smoking volunteers were exposed to dilute DE or filtered air for one hour whilst changes in heart rate were similar (P<0.028).

Results: Our results show unexpected haemodynamic responses to NE after exposure to dilute DE, with both attenuated vasopressor responses and an inhibitory effect on cardiac index. These novel findings suggest that DE inhalation alters the cardiovascular response to adrenergic stimulation, which could represent an effect on the autonomic nervous system.

385. Understanding disease and drug mechanisms

3446 The long-acting β2-agonist formoterol re-establishes the anti-proliferative effect of glucocorticoids in asthmatic airway smooth muscle cells (ASMC)

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Background: Asthma is characterized by an increased mass of ASMC which show increased proliferation in vitro. As previously reported, glucocorticoids do not have a significant anti-proliferative effect on ASMC of asthmatics while although their anti-inflammatory efficacy is maintained.

Methods: We assessed whether the addition of the long-acting β2-agonist formoterol modifies the anti-proliferative efficacy of glucocorticoids (budesonamide, budesonide, fluticasone). Primary human ASMC lines from asthmatics and controls were set up from bronchoscopic lung biopsies.

Results: Serum deprived sub-confluent cells were stimulated by 5% serum with or without a single drug or combination for a further 48 and 72 hrs. Serum alone increased cell proliferation in healthy control cells by 65% (48 hrs) and 81% (72 hrs); a significantly higher proliferation response was seen in asthmatic ASMC (82% at 48 hrs; 123% at 72 hrs). In the presence of different glucocorticoids alone serum-induced proliferation was significantly reduced in healthy cells (max. 48%) but not in asthmatic ASMC. Treatment with formoterol alone reduced serum-induced proliferation by 24% at any time point, with no differences between asthmatic and healthy ASMC. When formoterol was combined with fluticasone a 78% reduction of ASMC proliferation was achieved.

Conclusions: Our results show that the β2-agonist formoterol re-establishes the anti-proliferative effect of fluticasone in asthmatic airway smooth muscle cells. This synergistic action may exert an anti-remodeling effect on the asthmatic airway supporting the clinical benefit of combination therapy.

3447 A novel target of formoterol, a dual-specificity phosphatase DUSP4 on regulation of corticosteroid budesonide sensitivity

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Introduction: We previously reported that formoterol, a long-acting β2-adrenoceptor agonist, activated a serine/threonine protein phosphatase PP2A which is involved in the restoration of corticosteroid (CS) sensitivity by formoterol (Kobayashi et al ERJ 2009;34:583s). We explored other phosphatases and identified dual-specificity phosphatase DUSP4 as a possible novel target of formoterol.

Aims: To confirm that DUSP4 is activated by formoterol and is involved in regulation of CS sensitivity.

Methods: U937 monocytic cells were incubated with IL-2 and IL-4 for 48 h to induce CS insensitivity. CS sensitivity was determined by the CS budesonide ability to inhibit TNFα-induced IL-8 production and to translocate glucocorticoid receptor (GR) from cell cytoplasm to nucleus. Phosphatase activity of immunopurified DUSP4 was measured by fluorescence-based assay. The nuclear/cytoplasmic GR ratio and phosphorylation levels of GR,Ser237 and JNK1 by formoterol were assessed by western-blotting. In some experiments DUSP4 was knocked down by siRNA.

Results: Formoterol increased DUSP4 activity, which was reduced under IL-2/IL-4 exposure. Knock-down of DUSP4 reduced GR nuclear translocation and CS sensitivity. Knock-down of DUSP4 also abrogated the dephosphorylation of GR-Ser237 and JNK1 by formoterol - the effects involved in GR nuclear translocation and restoration of CS sensitivity.

Conclusions: Formoterol regulates sensitivity to budesonide through activation of DUSP4 which dephosphorylates JNK1 and GR, which may lead to dephosphorylation of GR-Ser237. This novel mechanism by formoterol may contribute to the clinical efficacy of combination of formoterol and budesonide.

3448 Tiotropium reduces established pulmonary inflammation in a 12 weeks cigarette smoke mouse model of COPD

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Rationale: Tiotropium bromide (Spiriva®) is the only marketed long acting anti-cholinergic for the treatment of chronic obstructive pulmonary disease (COPD).
3450 The pre-clinical pharmacology of the inhaled muscarinic antagonist GSK537319 predicts once-daily clinical dosing Dzinane I. Lanté, Mark A. Lannam, James J. Foley, Chris J. Dehaas, Charles J. Ketzer, Michael Salomon, William L. Runsey. Respiratory CEDO, GlaxoSmithKline, King of Prussia, United States

Introduction: GSK537319 is a new, long-acting muscarinic antagonist offering sustained 24-h bronchodilation currently in phase III clinical trials for COPD.

Objectives: To assess the pharmacology of GSK537319 in pre-clinical studies.

Methods/Results: In CHO cells transfected with recombinant human M3 receptors, GSK537319 demonstrated pD2 potency (~log pA2 = 23.5 pM) in an acetylcholine (ACh)-mediated Ca2+ mobilisation assay. Concentration-response curves indicated competitive antagonist with partial reversibility after drug wash out. Using isolated human bronchial strips in static tissue baths, GSK537319 was a potent, competitive antagonist (~log pA2 = 316 pM) vs carbachol. Superfusion of bronchial strips with carbachol containing buffer showed that GSK537319 was slowly reversible in a concentration-dependent manner (1–1000 nM). Time to 50% restoration of contraction at 10 nM was ~60 min (vs 413 min with topipramide, 10 mM). In conscious guinea pigs, GSK537319 dose-dependently blocked ACh-induced bronchodilation with long-lasting effect of action; a 2.5 g intratracheal dose elicited ~50% bronchoprotection for >24 h.

Conclusions: GSK537319 is a potent muscarinic antagonist that demonstrates slow reversibility at cloned human M3 receptors and at endogenous mAChR in isolated human bronchus. This profile translates into 24-h duration of bronchodilation in the clinic, suitable as a once-daily treatment for COPD.

Funded by GSK.

*Formerly at GSK.

3451 Synergistic bronchoprotective activity of the long-acting beta 2-agonist olodaterol with tiotropium: potential impact of chronic obstructive pulmonary disease (COPD) Anna Sola1,2,3, Michael Nyberg2,3, Christine Möller Westerberg2,3, Milos Tatar1, Barbara Fuchs1,2,3, Lisa Sjöberg1,2,3, Christine Möller Westerberg2,3, Gunnar Nilsson2.

Introduction: Muscarinic activation of human lung fibroblasts is associated with pathological remodelling in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD).

Aims: To investigate the in vitro effects of aclidinium bromide, a novel, long-acting muscarinic antagonist, on human lung fibroblast activation.

Methods: Lung fibroblasts, isolated from human bronchus, were pre-incubated with aclidinium (10^-5M-10^-7M), the ERK 1/2 inhibitor PD98059 (10^-6M) or the cAMP analogue dbcAMP (1nm) for 30 min and then exposed to carbachol (10^-7M) for 48 h. Collagen type I and alpha-smooth muscle actin (αSMA) expression were measured by RT-PCR, Western blot (WB) and immunofluorescence. ERK 1/2 phosphorylation was measured using intracellular cAMP levels by cAMP Biotrak enzyme immunoassay. Fibroblast proliferation was assessed using a BrDU kit, and fibroblast migration by wound closure assay.

Results: Aclidinium, PD98059 and dbcAMP attenuated carbachol-induced increases in αSMA and collagen type I mRNA and protein levels. Aclidinium and dbcAMP prevented carbachol-induced increases in phospho-ERK 1/2. Carbachol (10^-6M) prevented isoprenaline (1μM)-induced cAMP upregulation, which was completely reversed by aclidinium 10^-5M. Carbachol-dependent increases in lung fibroblast proliferation (2-fold) were reduced by aclidinium 10^-5M (1.1-fold), PD98059 (1.3-fold) and dbcAMP (1.2-fold). Aclidinium 10^-6M, PD98059 and dbcAMP reduced αSMA and collagen type I wound closure by 30%, 28% and 40%, respectively.

Conclusions: Aclidinium blocks carbachol-induced lung fibroblast proliferation probably by a direct effect at muscarinic receptors. Aclidinium may alleviate fibroblast activation in patients with asthma and COPD.

The cyclooxygenase (COX) product prostaglandin (PG) E2 is known to act bronchoprotective in asthmatics. Recent preclinical studies identified the COX-terminal microsomal PGE synthase-1 to contribute to the formation of protective PGE2. This study investigated whether the release of bronchoprotective COX products is mast (MC) dependent. Chronic allergic airway inflammation in mice was induced by ovalbumin/chloroform and continued during 90 days. COX-inhibition with diclofenac (DFC) was performed. Airway hyperresponsiveness (AHR) was assessed applying forced-oscillation technique in response to methacholine. Contribution of MC-COX-products to AHR was resolved by comparingWSC (MC-deficient) to C57BL/6 wild type (WT) mice (MCs around central airway). Central airway resistance, Rn, was reduced in allergen-challenged WT mice and increased in WT-DFC [cmH2O*ml^-1*sec^-1*cm^-5] (p<0.04). Ws displayed comparable resistance [1.7±0.1 cmH2O*ml^-1*sec^-1*cm^-5] as WT-DFC. Rn in Ws was not changed after treatment [1.9±0.2 cm]. Both mouse strains lacked MCs in peripheral lung tissue. Consequently, tissue resistance was not changed in WT and Ws [8.5±0.5 vs 7.8±0.6], nor after treatment [WT-DFC 7.8±0.5, Ws-DFC 7.6±0.6]. Although a shift in baseline tissue elastance was observed between WT and Ws [21.9±1.4 vs 17.7±2.4, p=0.02], treatment did not affect baseline [WT-DFC 21.4±1.2, Ws-DFC 17.6±1.09], nor was the reactivity changed.

The data indicates that the bronchoprotective role of PGE2 is MC dependent. It remains to be seen if this is due to PGE2 or other COX products released by MCs, or if modulating COX products are released by other cells and play role in MC activation.

3452 Mast cell generated cyclooxygenase products protect airway hyperresponsiveness in a model of chronic asthma Barbara Fuchs1,2,3, Lisa Sjöberg2,3, Christine Möller Westerberg2,3, Maria Ekofsk1, Linda Swedin5, Sven-Erik Dahlén1,1, Mikael Adner1,1, Gunnar Nilsson2.

Introduction: In vitro effects of aclidinium bromide, a novel, long-acting muscarinic antagonist, on human lung fibroblast activation.

Methods: Lung fibroblasts, isolated from human bronchus, were pre-incubated with aclidinium (10^-5M-10^-7M), the ERK 1/2 inhibitor PD98059 (10^-6M) or the cAMP analogue dbcAMP (1nm) for 30 min and then exposed to carbachol (10^-7M) for 48 h. Collagen type I and alpha-smooth muscle actin (αSMA) expression were measured by RT-PCR, Western blot (WB) and immunofluorescence. ERK 1/2 phosphorylation was measured using intracellular cAMP levels by cAMP Biotrak enzyme immunoassay. Fibroblast proliferation was assessed using a BrDU kit, and fibroblast migration by wound closure assay.

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Conclusions: Aclidinium blocks carbachol-induced lung fibroblast proliferation probably by a direct effect at muscarinic receptors. Aclidinium may alleviate fibroblast activation in patients with asthma and COPD.

The cyclooxygenase (COX) product prostaglandin (PG) E2 is known to act bronchoprotective in asthmatics. Recent preclinical studies identified the COX-terminal microsomal PGE synthase-1 to contribute to the formation of protective PGE2. This study investigated whether the release of bronchoprotective COX products is mast (MC) dependent. Chronic allergic airway inflammation in mice was induced by ovalbumin/chloroform and continued during 90 days. COX-inhibition with diclofenac (DFC) was performed. Airway hyperresponsiveness (AHR) was assessed applying forced-oscillation technique in response to methacholine. Contribution of MC-COX-products to AHR was resolved by comparing WSC (MC-deficient) to C57BL/6 wild type (WT) mice (MCs around central airway). Central airway resistance, Rn, was reduced in allergen-challenged WT mice and increased in WT-DFC [cmH2O*ml^-1*sec^-1*cm^-5] (p<0.04). Ws displayed comparable resistance [1.7±0.1 cmH2O*ml^-1*sec^-1*cm^-5] as WT-DFC. Rn in Ws was not changed after treatment [1.9±0.2 cm]. Both mouse strains lack MCs in peripheral lung tissue. Consequently, tissue resistance was not changed in WT and Ws [8.5±0.5 vs 7.8±0.6], nor after treatment [WT-DFC 7.8±0.5, Ws-DFC 7.6±0.6]. Although a shift in baseline tissue elastance was observed between WT and Ws [21.9±1.4 vs 17.7±2.4, p=0.02], treatment did not affect baseline [WT-DFC 21.4±1.2, Ws-DFC 17.6±1.09], nor was the reactivity changed.

The data indicates that the bronchoprotective role of PGE2 is MC dependent. It remains to be seen if this is due to PGE2 or other COX products released by MCs, or if modulating COX products are released by other cells in response to MC activation.

3453 Antifluorescent activity of (-) menthol mediated by nasal trigeminal TRPM8 receptor: Jana Plevkova1, Brendan J. Canning2, Ivan Polacki3, Mariana Brozmanova1, Milos Tata1.

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(-) Menthol, main component of the peppermint is exploited in many over-the-
counter drugs for common cold and cough. It has been reported that (-) menthol has an antitussive effect in humans and animals. However, there are conflicting evidence against that statement and also cases report of respiratory failure induced by menthol in kids. Based on the recent data about the distribution of the TRPM8 – menthol receptors expressing neurons in the upper airways, and their low proportion within the vagal nerves in lower airways we suppose, that effect of (-) menthol on cough could be mediated by TRPM8 expressed on nasal afferents. To test this hypothesis a segmental airway challenges with (-) menthol were performed in anaesthetized guinea pigs (nose, trachea and lower airways were separately treated by menthol). A dose–response curves (DRC) were constructed according the method described by Canning et al., 2006. The DRC were compared to control provocations. The (-) menthol applied topically to the trachea does not influence cough significantly. (-) menthol vapors applied directly to lower airways via cannula resulted to the tendency to facilitate cough, with visible signs of increased mucus output, loaded breathing and wheezing. The antitussive effect of menthol was observed only in the group treated by nasal (-) menthol vapors, which reduced cough response to CA significantly comparing to control response p < 0.001.

Our results correspond with the data describing the TRPM8 distribution in the respiratory tract, and may contribute to explanation adverse effects induced by menthol inhalation in kids. Supported:VEGA 1/0031/11.

386. Obstructive sleep apnoea as a comorbidity

P3454
Optimizing the screening of OSA in patients undergoing bariatric surgery
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Obstructive Sleep Apnea (OSA) is common in patients waiting bariatric surgery (BS). International consensus recommend OSA preoperative assessment to avoid perioperative complications. Full-night polysomnography (PSG) is the standard diagnostic method but it is expensive and time-consuming. The aim of the study was to select by a simple predictor model, those patients who merit treatment prior BS.

Methods: A prospective cross-sectional study was conducted in 158 consecutive bariatric subjects. PSG was performed in all. The outcome variable was severe OSA defined as apnea-hypopnea index (AHI) ≥30. Predictive models were constructed using multivariate logistic regression analysis. The best model was selected depending on the area under receiver operating characteristic curve (AUROC).

Results: The first model indentified four independent predictive factors of AHI ≥30: age, waist-to-hip ratio, systolic blood pressure and witnessed apneas (Apn) with predictive values: sensitivity (Se) 78%, Specificity (Sp) 81%, AUROC 0.81. The second model (clinical plus ODI1%) indentified two independent predictive factors (AHI, ODI%) with predictive values: Se 98%, Sp 89%, AUROC 0.95. We proposed a two-step screening: first, applying the clinical model and then, the second model; 47% of subjects would be rule out (21% and 26% by the first and second steps). Only 53% would require PSG prior BS.

Conclusions: The proposed two-step model could be useful to optimize the screening of severe OSA in bariatric subjects improving the limiting resources of PSG.

P3455
Is lung transplantation a cause of sleep apnea hypopnea syndrome?
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Aims: To analyze the presence of Sleep Apnea Hypopnea Syndrome (SAHS) in a cohort of patients before and after lung transplantation (LT).

Methods: All consecutive LT recipients with at least 2 polysomnographies (PSG) at 6 weeks of commencement of rhGH in a tertiary paediatric sleep setting.

Results: The prevalence was 30% (n=3) pre-LT, 80% (n=8) at the first PSG after LT, and 40% (n=4) at the second one. There were significant differences between mean AHI in the pre-LT sleep study and AHI in the first study after LT, but not with the one after 12 month of follow up. The data are shown in the figure.

P3456
Obstructive sleep apnea syndrome (OSAS) and asthma in a general population
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Background: Several studies have investigated associations between OSAS and asthma, with inconsistent results.

Aim: To determine if asthma and bronchodilator reactivity (BDR) are independent risk factors for OSA in the Norwegian population.

Methods: An age and sex stratified random sample of all adults aged 47-48 and 71-73 living in Bergen, Norway, were invited to a cross-sectional survey. The 3506 attendants (69%) completed a questionnaire including symptoms of OSAS. Subjects were classified as having OSAS if they reported snoring, breathing cessations, and daytime sleepiness using the Karolinska Sleep Questionnaire, previously validated against polysomnography. Subjects were classified as asthmatics if they had ever received a doctor’s diagnosis of asthma and currently were on antiasthmatic medication.Spirometry including bronchodilator test inhaling 400 μg Salbutamol was performed by all subjects. Two logistic regression models were fitted with OSAS as the outcome variable; one with current asthma and one with BDR as main explanatory variable. Both models included age, sex, body mass index (BMI), waist-hip ratio and smoking.

Results: The prevalence of OSAS was 4.5% (147/3289) in subjects without asthma, and 9.7% (21/217) in subjects with asthma [P=0.001]. Subjects with current asthma had an increased risk for OSA with an OR of 2.2 (1.3, 3.7), after adjustment for all confounders. BDR, measured by difference in ml between pre- and post-bronchodilator spirometry, did not seem to confer increased risk for OSAS; OR 1.0 (0.3, 3.8).

Conclusions: Our study confirms asthma as an independent risk factor for OSAS. We were not able to demonstrate a relationship between bronchodilator reactivity and OSAS.

P3457
Sleep disordered breathing in Prader Willi syndrome post recombinant human growth hormone therapy
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Introduction: Recombinant human growth hormone (rhGH) is licensed for treatment in Prader Willi Syndrome (PWS) for improvement of body composition, height velocity, mobility, behaviour and quality of life. Sleep disordered breathing (SDB) disorders are common in individuals with PWS. It has been suggested that rhGH exacerbates SDB.

Aim: To identify PWS children who have changes in SDB on polysomnography (PSG) at 6 weeks of commencement of rhGH in a tertiary paediatric sleep setting.

Methods: We retrospectively reviewed PWS patients who underwent PSG pre and
6 weeks post commencement of rhGH. The PSG was conducted in a sleep lab using standardized procedure and reported by a sleep physician.

Results: We studied 26 patients (13 Boys and 13 Girls) with age range between 1.6 to 17.9 years. 16 patients (61.5%) had normal PSG study indicating no deterioration in SDB since commencing on rhGH, 5 patients (19.2%) had mild increase in Apnoea Hypopnoea Index (AHI). 1 patient (3.8%) required an increase in supplemental airway pressure (CPAP) treatment and 4 patients (15.4%) were advised to cease rhGH treatment as PSG showed significant increase in AHI since rhGH commencement.

Conclusion: 80% of our PWS patients on rhGH had either no evidence of change in SDB six weeks post rhGH treatment or mild increase in AHI. 19.2% (5 Patients) in which 4 patients (15.4%) studied ceased rhGH and in 1 (3.8%) NIV support was increased.

P3458
Periodic breathing and oxygenation pattern depending on severity of bronchopulmonary dysplasia
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Objective: Periodic breathing (PB) is a common breathing pattern in premature infants. Our aim was to study PB occurrence and its impact in oxygenation in infants with moderate and severe bronchopulmonary dysplasia (BPD) compared to infants without BPD.

Methods: We performed pneumography on 25 premature infants with BPD (1 case of severe, 8 of moderate, and 16 of mild BPD) and 25 non-BPD premature comparable in gestation age (26-30 weeks). Infants were examined 1-3 times at ages of less than 29 days, 29-50 days, more than 50 days. Incidence of main neurologic abnormalities appeared not to differ among groups.

Results: Incidence and duration of PB did not differ in infants with mild BPD and without BPD at all ages. Infants with moderate to severe BPD demonstrated no PB during first 28 days, lesser incidence of PB at 29-50 days (1 of 3 infants), lesser duration of PB at 50 days and older (4.3±3.1% of recording length) compared to infants with mild BPD (8 of 10 infants; 18.3±6.7%, respectively; P<0.05) and without BPD (17 of 18 infants; 13.3±5.3, respectively; P<0.05).

Conclusion: Infants with mild BPD seem to have more active peripheral chemoresponsiveness compared to premature with moderate to severe lung disease. PB may be associated with significant desaturations in infants with BPD regardless of its severity.

P3459
Effects of sleep disordered breathing, asthma and socio-economic status on behavioural parameters in children
Yasemin Golokmen1, Refta Erzu1, Ayse Rodopman Arman1, Pınar Ay1, Ahmet Topuzoglu1, Fatih Telrik1, Bulent Karadag1, Fazilet Karakoc1, 1 Paediatric Pulmonology, Marmara University, Istanbul, Turkey; 2 Child Psychiatry, Marmara University, Istanbul, Turkey; 3 Public Health, Marmara University, Istanbul, Turkey

Background: Inner-city children with asthma have increased prevalence of sleep disordered breathing (SDB) and these children have more pronounced behavioral problems.

Aim: To study the effect of asthma and SDB on behavior in children by socio-economic status (SES).

Methods: This cross sectional study was performed in 6 primary schools; 3 with low and 3 with high SES. These schools were determined by a previous study which evaluated the SES of students. All children in the 1st to the 4th grades were included. ISAAC questionnaire for asthma, pediatric sleep questionnaire for SDB and a standardized SES questionnaire were completed by the parents.

Results: 1383 children (51% female) were included. Mean age was 8.7±1.1 years. Rates of ever and current wheezing were 25.8% (95%CI: 23.5-28.2%) and 19.8% (95%CI:17.7-21.9), respectively. 11.4% (95%CI:8.13-12.2%) children had doctor diagnosed asthma and 7.1% (95%CI:5.8-8.5) had SDB. Children attending schools in poor neighbourhoods tended to have higher rates of SDB (p<0.05). Although children in both groups had similar rates of ever and current wheezing, those with lower SES had less doctor diagnosed asthma (p<0.05). Children with SDB had increased risk of ever and current wheezing and risk increased in children with lower SES. Presence of SDB increased the risk of ever wheezing among children with low and high socio-economic status with an OR of 4.4 and 3.2, respectively (95%CI:1.05-15).

Conclusion: SDB is more common in children with lower SES. Children with SDB have higher rates wheezing and risk increases in children with lower SES.

P3461
Obstructive sleep apnoea syndrome and insomnia: The development of insomnia symptoms with CPAP treatment
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Rationale: Insomnia is frequently reported in obstructive sleep apnoea syndrome (OSAS) patients due to the high prevalence of both diseases and, potentially, a causal relationship between them.

Objective: To assess the evolution of insomnia under long-term continuous positive airway pressure (CPAP) treatment.

Methods: Eighty apnoic patients (age = 54.9±10.6 years, respiratory disturbance index = 45.0±24.6/h) on CPAP were followed prospectively for 24 months. Depressive symptom was assessed at baseline (T0) with the ZDS scale, and assessment of insomnia and sleep quality used the Insomnia Severity Index (ISI) (an ISI ≥ 14 defining insomnia) and the Pittsburgh Sleep Quality Index (PSQI) at T0 and T24. A multivariate correlation analysis identified the major explanatory factors for the ISI at T24.

Results: The median ISI was 14 at T0 and 6 at T24. The ISI (13.7±4.7) at T24 was significantly lower than at T0 (15.5±5.5, p=0.0001) for the patients as a group. Forty-three subjects (54%) had insomnia at T0, and 14 (17.5%) were still insomniac at T24 (p=0.0001). The ISI≥7 (p=0.41), PSQI≥15 (p=0.40), antidepressant use (p=0.36), depression score (p=0.33) and female gender (p=0.28) correlated with ISI at p<0.01, but CPAP compliance did not.

Conclusion: Insomnia was no longer measurable with CPAP treatment in two-thirds of initially insomniac patients. Residual insomnia was associated with high levels of initial insomnia and depressive symptoms.

P3462
Are sleep, nocturnal breathing and daytime performance impaired at moderate altitude?
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Background: There are concerns that even mild hypoxia at altitude has unfavorable health effects. The current study evaluates the hypothesis that sleep quality and daytime performance of lowlanders are impaired during a stay at moderate altitude.

Conclusion: Increased rates of externalizing and internalizing problems in inner-city primary school children with SDB might reflect a negative impact on overall neurobehavioral health. Being male, coming from lower SES, and the presence of both wheezing and SDB might increase negative behavioral problems.

615s
Methods: Fifty healthy men, mean ± SD age 26 ± 9 y, living at <600m, were studied at Zurich (490m) and while staying in the Swiss Alps at Davos Wolfang (1630m, 2 days) and Jakobshorn (2590m, 2 days), in randomized order. Sleep studies, psychomotor vigilance tests (PVT), snow board simulator tests and questionnaire evaluations were performed at all locations.

Results: Compared to 490m, sleep studies at altitude revealed reduced oxygen saturation, a higher central apnea/hypopnea index and reduced slow wave sleep. Multiple logistic regression did not show an independent effect of altitude on reaction times in PVT and snowboard simulator when controlled for various confounders.

Conclusion: In healthy men, mild nocturnal hypoxemia and periodic breathing at moderate altitude are associated with subtle sleep disturbances but neither subjective sleep quality nor psychomotor vigilance during daytime are impaired.

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P3463
Prevalence of thyroid disease in patients with obstructive sleep apnea
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Background: Previous studies have reported conflicting results with regard to thyroid disease in obstructive sleep apnea (OSA) patients.

Methods: To determine the prevalence and predictors of thyroid disease in OSA patients.

Objective: Determined the prevalence of thyroid disease in OSA patients.

Methods: Consecutive patients who were referred for an overnight polysomnography (PSG) in the study period underwent serum TSH and thyroxine (FT4) measurement within 4 weeks of PSG using the electrochemiluminescence immunoassay method. Standard definitions were used to define clinical hypothyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism.

Results: Of 271 patients with OSA and a mean age of 50±11.8y, 120 (44.3%) were female. The prevalence of newly diagnosed clinical hypothyroidism was 5%. There were no cases of clinical or subclinical hyperthyroidism in the studied group. Female gender was the only predictor of subclinical hypothyroidism.

Conclusion: The prevalence of newly diagnosed clinical hypothyroidism was very low in OSA patients who are followed up for their sleep problems. There was no correlation between AHI and the severity of sleep apnea (p=0.328). The analysis of the hypogram showed that sleep fragmentation, characterized by arousal index (AI), was a significant impact on the sleep apnea (p=0.048, r=0.265). Another important factor that determines daytime affective status was nocturnal hypoxemia (p=0.05, r=0.265).

Results: Thirty of the patients (51,7%) had depressive symptoms. There was no correlation between AHI and the severity of depression (p=0.328). The analysis of the hypogram showed that sleep fragmentation, characterized by arousal index (AI), was a significant impact on the sleep apnea (p=0.048, r=0.265). Another important factor that determines daytime affective status was nocturnal hypoxemia (p=0.05, r=0.265).

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Background: Sleep apnea is a common sleep disorder that affects millions of people worldwide. It is characterized by repeated episodes of apnea (cessation of breathing) and hypopnea (reduction in airflow) during sleep, leading to sleep fragmentation and daytime sleepiness. The impact of sleep apnea on sleep quality and quality of life is well-documented, with significant implications for overall health and well-being. However, the prevalence and clinical significance of depressive symptoms in patients with obstructive sleep apnea (OSA) have not been thoroughly explored.

Methods: A cross-sectional study was conducted to assess the prevalence of depressive symptoms in patients with OSA and to explore potential correlations between sleep apnea severity and depressive symptoms.

Results: A total of 271 patients with OSA and a mean age of 50±11.8 years were included in the study. The prevalence of newly diagnosed clinical hypothyroidism was 5%. There were no cases of clinical or subclinical hyperthyroidism in the studied group. Female gender was the only predictor of subclinical hypothyroidism.

Conclusion: The prevalence of newly diagnosed clinical hypothyroidism was very low in OSA patients who are followed up for their sleep problems. There was no correlation between AHI and the severity of sleep apnea (p=0.328). The analysis of the hypogram showed that sleep fragmentation, characterized by arousal index (AI), was a significant impact on the sleep apnea (p=0.048, r=0.265). Another important factor that determines daytime affective status was nocturnal hypoxemia (p=0.05, r=0.265).

Results: Thirty of the patients (51.7%) had depressive symptoms. There was no correlation between AHI and the severity of depression (p=0.328). The analysis of the hypogram showed that sleep fragmentation, characterized by arousal index (AI), was a significant impact on the sleep apnea (p=0.048, r=0.265). Another important factor that determines daytime affective status was nocturnal hypoxemia (p=0.05, r=0.265).
P3468

Are upper airways resistance syndrome and obstructive sleep apnea a side-effect of oral cancer therapy?

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Background: Reconstruction surgery and radiotherapy cause changes in airway calibre and tone which may lead to Upper Airways Resistance Syndrome (UARS) and Obstructive Sleep Apnea (OSA). We aimed to study the prevalence of UARS and OSA in treated Oral Cancer patients.

Methodology: 78 patients (69 males, 9 females, mean age 49 years) treated for Oral Cancer were administered the Epworth Sleepiness Scale (ESS). Patients' perception of sleep quality (SLq) and mental health status were noted from Mental Health Questionnaire (GHQ), Perceived Stress Scale (PSS), as well as General Health Questionnaire (GHQ), Perceived Stress Scale (PSS), as well as Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Quality of Life Questionnaire (QLQ-H&N35) and all underwent Polysomnography. They were categorised on the basis of Respiratory Disturbance Index (RDI) into Normal (RDI <5/h), UARS (RDI 5-15/h), OSA (RDI >15/h) and Sleep Disordered Breathing (SDB) where (SDB=UARS+OSA; RDI >5/h).

Results: 66 patients underwent surgery with adjuvant (chemo)radiotherapy and re-annotation of sleep caused in OSA patients. Perinatal sleep apnea is associated with down-regulation of pro-inflammatory proteins (Cox-2) induced in obstructive sleep apena syndrome (OSAS) severity and sleep structure.

P3494

Microparticles from OSA patients induce hyper-reactivity through up-regulation of pro-inflammatory proteins

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Obstructive sleep apnea (OSA) is characterized by repetitive upper-airway obstruction during sleep, which is associated with oxygen desaturation and sleep disruption. It has been shown that level of circulating microparticles (MPs), vesicles released from plasma membrane during cell activation and apoptosis, is altered in OSA patients and contribute to endothelial dysfunction. However, their participation to reactivity in response to vasoconstrictor agonists has not yet been assessed. Two anti-matched groups of patients undergoing polysomnography for OSA were compared: 15 patients with an apnea-hypopnea index (AHI)<5 events/h were included in the OSA group and 17 control subjects with an AHI<5. MPs obtained from blood either from OSA patients or control subjects, or a vehicle were injected iv to mice. Injection of MPs from OSA patients induced vascular hyper-reactivity in response to serotonin in aorta. Interestingly, hyper-reactivity was not affected by inhibition of nitric oxide (NO)-synthase (NOS) compared to control subjects and was associated with downregulation of end (FSFI), Female Sexual Distress Scale (FSDS), and decreased NO production. The non selective cyclooxygenase (COX) inhibitor or the selective

COX-2 inhibitor reduced serotonin-induced hyperreactivity in aorta from OSA MP-treated mice. This effect was associated with increased COX-2 and NF-kB expressions. These data provide evidence that circulating MPs from OSA patients induce ex vivo vascular hyperreactivity by a combination of upregulation of proinflammatory proteins and a reduced ENOS activity and NO production. These results highlight vascular dysfunction induced by MPs that might participate to events associated in OSA.
387. Challenges in chronic disease management: helping individuals with chronic lung disease remain stable

P3472 Late-breaking abstract: Comparison of respiratory symptoms in chronic pulmonary obstructive disease and restrictive ventilatory impairment according to disease stage: The PLATINO study in Latin America

Introduction: Obstructive pulmonary disease presents defined symptoms such as cough, dyspnea, sputum and wheezing. Symptoms of restrictive ventilatory impairment are less well defined.

Objective: Compare the occurrence of respiratory symptoms in chronic obstructive pulmonary disease with the ones presented by individuals with restrictive impairment in the different stages of the disease.

Methods: Between 2002 and 2004, individuals over 40 years of age from five cities in Latin America were analyzed and had a pre post-bronchodilator spirometry done and reported their respiratory symptoms.

Results: N= 5315: 260 (4.9%) - restriction impairment and 759 (14.4%) - COPD diagnoses. Patients with COPD coughed more (31.4% vs 23.5%; OR 1:36: 1.05, 1.74) and had more sputum (28.3% vs 21.9%; OR 1:10: 1.0, 1.68). No difference was seen in dyspnea (OR:0.86 (0.69,1.06) between the two groups. Comparing the different stages of disease, at moderate stage: COPD patients presented more cough than those with restrictive impairment (40.5% vs 27.3%; OR 1.53: 1.07,2.20) and more sputum (36.6%) vs 23.6%; OR 1.57: 1.07-2.30); moderate, severe and very severe stages: COPD had more wheezing episodes than those with restrictive disease. Regarding dyspnea, it was more intense in patients with mild restriction than in those with mild COPD (43% vs 6%; OR 1:11:1.0, 2.12).

Conclusions: Cough and sputum are more frequent in patients with COPD than those with restrictive ventilatory impairment. Dyspnea is a symptom more pronounced in patients with restrictive impairment compared with individuals with COPD in early stages of the disease.

P3473 Mobile device usability to support chronic obstructive pulmonary disease management

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COPD generates a serious burden on healthcare systemic. Telemedicine contribute to an efficient use of healthcare resources reducing number of non-scheduled visits. Are lacking studies assessing patients and healthcare provider’s satisfaction on these new approaches. The aim of the study was to determine the usability & satisfaction of COPD patients and professionals with a mobile device to support COPD management. A mobile system was offered during two weeks to 17 COPD patients (FEV1 47.2% of predicted age 65.14) patients answered the EuroQol questionnaire every day and used pulse oximetry during any exercise session at home setting. Data was collected & checked in a technological platform. Patients and professionals accomplished a usability & satisfaction questionnaire at the end of the study. 18% of patients refused and 65% finished the program. 83% felt safer during exercise and more controlled by professionals. 61% indicated that the device makes them do more physical activity. Lack of acceptance to undergo the study and drop-outs were associated with personality disorders (p<0.05). All patients evaluated positively the usability of the device and as a motivator to perform exercise. All professionals evaluated it as a useful tool to enhance life-style and to support their remote management.

Transfer of data between a mobile device and a digital platform is feasible for COPD patients. Remote monitoring of physical activity can enhance motivation to perform sustainable exercise and seems to show high grade of adherence. Long-term follow-up of a large number of patients will be needed to define effective home-based services to enhance management of COPD patients. Supported by Nexo UE - FP7 (CIP-ICT) 225025; FIS-Fit.

P3474 Access and use of communication technologies in patients with chronic obstructive pulmonary disease

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Information and Communication Technologies (ICT) have proven useful to enhance citizens’ active involvement in several domains, including healthcare. Despite access to ICT is widespread across Europe, usability of ICT by elderly patients with chronic conditions remains controversial. The research was conducted within the frame of NEXES, an EU project designed to assess extensive deployment of integrated care services supported by an information technology platform (Linkcare®). The study explores current habits/attitudes of COPD patients concerning the use of mobile phones and Internet.

Prior to the initiation of the wellness and rehabilitation program in NEXES, we conducted a phone interview to 68 COPD patients (FEV1 P50-P95: 21-74%pred; age 65-95: 54-78 years) to investigate their attitude towards telemedicine. 41% of the patients use Internet and 91% use mobile phones. 58% of all subjects have internet access at home. The main reason for not using Internet is a poor knowledge on how to use it (76% of non-users). But, 55% of the non-Internet users are interested in learning how to use it. Among the Internet users, 89% have access to e-mail and 46% of them participate in social networks. 62% of patients send SMS’s and 15% send files by mobile phones. The use of mobile phones correlates with age (p<0.04) whereas Internet correlates with educational level (p<0.001), but not with disease severity or aerobic capacity.

The percentage of COPD patients using Internet and mobile phone is similar to the general population of the area for the same range of age. Disease severity or presence of COPD generate a serious burden on healthcare system. Telemedicine contribute to an efficient use of healthcare resources reducing number of non-scheduled visits. Are lacking studies assessing patients and healthcare provider’s satisfaction on these new approaches. The aim of the study was to determine the usability & satisfaction of COPD patients and professionals with a mobile device to support COPD management. A mobile system was offered during two weeks to 17 COPD patients (FEV1 47.2% of predicted age 65.14) patients answered the EuroQol questionnaire every day and used pulse oximetry during any exercise session at home setting. Data was collected & checked in a technological platform. Patients and professionals accomplished a usability & satisfaction questionnaire at the end of the study. 18% of patients refused and 65% finished the program. 83% felt safer during exercise and more controlled by professionals. 61% indicated that the device makes them do more physical activity. Lack of acceptance to undergo the study and drop-outs were associated with personality disorders (p<0.05). All patients evaluated positively the usability of the device and as a motivator to perform exercise. All professionals evaluated it as a useful tool to enhance life-style and to support their remote management.

Transfer of data between a mobile device and a digital platform is feasible for COPD patients. Remote monitoring of physical activity can enhance motivation to perform sustainable exercise and seems to show high grade of adherence. Long-term follow-up of a large number of patients will be needed to define effective home-based services to enhance management of COPD patients. Supported by: UE – FP7 (CIP-ICT) 225025.

P3475 Evaluation of a web based home training program for COPD patients: A controlled trial

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Introduction: An important aim of rehabilitation of patients with COPD is to support them in acquiring and maintaining an active lifestyle. Dependent on their mobility to train, patients visit the rehabilitation center 2 or 3 times a week. It is hypothesized that a web based home training program, with exercise videos and a videoconference module can increase the efficiency and effectiveness of this rehabilitation program.

Aim and objective: To evaluate a web based home training program for COPD patients in terms of user experience (satisfaction and usability) and clinical benefits (changes in subjective perceived and objective measured health status: dyspnea and fatigue (VAS), CRQ and Six Minute Walk Test).

Methods: COPD patients were divided into a control and an intervention group. Patients of the control group followed the traditional rehabilitation program. Patients of the intervention group followed the same program but a web based home training program was provided as addition (for those visiting rehabilitation center 2 times a week) or as part replacement (for those visiting rehabilitation center 3 times a week). At baseline and after intervention measurements were obtained.

Results: Preliminary data analysis (n=23) shows that patients are satisfied with the web based home training program and rated its usability as good. The degree of clinical benefit of the intervention group (n=23) is similar to the progression made by the group (n=20) after rehabilitation.

Conclusions: Based on preliminary results, a web based home training program seems to have potential to treat patients in their own environment under professional supervision.

P3476 Fit for flight? An investigation into awareness of air travel recommendations among patients with respiratory disease

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Objective: To investigate awareness of air-travel guidelines among patients with respiratory disease.

Background: While the population has aged and prevalence of respiratory disease has risen, air travel has increased dramatically in the UK. A significant proportion of flight-related emergencies may be of respiratory origin.

Method: 64 respiratory patients completed questionnaires based on British Thoracic Society (BTS) guidelines, screening for awareness and experience of air travel. Pulse oximetry readings were performed and, where appropriate, frequency was recorded. Frequency data was analysed in StatsDirect, using Exact (Clopper-Pearson) 95% Confidence Intervals. Enquires about in-flight oxygen where made to 8 airlines.

Results: 72% of patients were aware of air travel guidelines. Of patients who deemed themselves fit to fly, 4% would require in-flight oxygen and 37.5% would be likely to require oxygen on flights lasting over 2 hours. Among patients planning to fly, 87.5% had never been offered pre-flight respiratory tests and 25% had suffered in-flight respiratory problems.

Conclusion: Awareness of air travel guidelines among respiratory patients is low and poses a significant health risk. Patients are inadequately offered pre-flight
respiratory tests and availability of in-flight oxygen varies widely between airlines and is, when offered, an expensive service. This study calls for greater recognition of air travel with respiratory disease among patients, physicians and airlines alike.

P3477 Air travel and COPD: Exercise SpO2 and walking distance as predictors for in-flight desaturation Anne Edvardsen1, Aina Akerø2, Carl Christian Christensen3, Morten Ryy1, Ole Henning Skjønberg2 1Department of Respiratory Physiology, Glimtetrøenkniven, Hakadal, Norway; 2Department of Pulmonary Medicine, Oslo University Hospital Ullevål, University of Oslo, Oslo, Norway

Background: Supplemental oxygen during air travel is recommended when in-flight PaO2 is expected to fall below 6.6 kPa in patients with lung disease. Sea level oxygen saturation falls to near oximetry saturation in altitude where supplemental oxygen has proven inadequate, as a predictor of in-flight hypoxemia, and it has been suggested that exertional flight PaO2 is expected to fall below 6.6 kPa in patients with lung disease. Sea level SpO2 can be measured to quantify the impact of comorbidities in COPD patients in research and practice.

Aim: The study aimed to evaluate if exertional desaturation and walking distance during a 6-min walk test (6MWT) might help predicting in-flight hypoxemia and thereby the need for in-flight oxygen in patients with COPD.

Methods: COPD patients referred to hypoxia-altitude simulation test (HAST) were consecutively included. Lung function tests, blood gas measurement, 6MWT, and HAST were performed. Seventy-four COPD patients (42% men) were included, mean (SD) age 65 (8) years, FEV1, 41 (13)% predicted. SpO2 baseline was 93 (3)% PaO2 HAST 6.3 (0.6) kPa, nadir SpO2 6MWT 83 (6)% nadir SpO2 6MWT and walking distance correlated with in-flight PaO2 (r=0.49, p<0.001) and r=0.27, p=0.007 respectively. ROC analysis with nadir SpO2 6MWT against PaO2 HAST ≤ 6.6 kPa gave an area under the curve of 0.786 and suggested that the cut-off yielding greatest accuracy for an in-flight PaO2 ≤ 6.6 kPa was a SpO2 6MWT below 85% (sensitivity 85%, specificity 69%). Walking distance had no prognostic value for in-flight PaO2 in the ROC analysis.

Conclusions: In patients with COPD, exercise desaturation below 85% suggests that in-flight oxygen might be needed. As a supplement to sea level SpO2, exercise desaturation might be useful in the initial pre-flight screening.

P3478 Deployment of integrated care services for patients with long-term oxygen therapy (LTOT): Role of frailty Carme Hernandès1, Enric Duran-Tauleria2, Silvia Valls1, Jesus Aibar1, Jordi Sarroca3, Nestor Soler4, Ida de Godoy5, Victor Castillo6, Alvar Aguisti7, Josep Roca2 1Integrated Care Unit, Hospital Clinic, Ciberes, IDIBAPS, Univ. Barcelona, Barcelona, Spain; 2Epidemiology Unit, PAMEM-IDIM, Barcelona, Spain; 3Hospital Clinic, IDIBAPS, Univ. Barcelona, Barcelona, Spain

Patients receiving LTOT are frequent users of healthcare services. Pilot studies have shown that Integrated Care Services (IC) reduce hospitalizations in these patients and have also identified that deployment of IC requires an operational definition of ‘IC’ and specific criteria for stratification of patients.

Objective: To characterize the risk profile of LTOT patients in an urban area of 540,000 inh in order to allow the design of a one-year follow-up RCT to assess deployment of IC tailored by patient’s frailty

Methods: Observational study examining 751 patient’s records. We planned three factors aiming at enhancing quality of LTOT.

Factors related with organization of healthcare services had impact on LTOT adherence (OR 0.45 [0.22–0.91]).

Conclusions: The study provides the rationale for future actions on modifiable factors aiming at enhancing quality of LTOT.

P3479 Development of a comorbidity index that reflects health-related quality of life in patients with COPD Anja Anja Frey1, Patrick Magguensturm1, Lara Siebeling2, Marco Zoller3, Cynthia Boyd4, Gerben ter Riet5, Milo Puhan1,2,3 1Horten Centre, University of Zurich, Zurich, Switzerland; 2Department of General Practice, University of Amsterdam, Amsterdam, Amsterdam, Netherlands; 3Department of General Practice, University of Zurich, Zurich, Switzerland; 4Department of Geriatrics, Johns Hopkins Hospital, Baltimore, United States; 5Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States

Background: In COPD research little consideration is currently given to the impact of co-existing comorbidities, which is partly due to the absence of an index that would quantify their impact. We developed a COPD comorbidity index that quantifies the impact on health-related quality of life (HRQL).

Methods: Using data from 411 Swiss and Dutch COPD patients with GOLD stage ≥2 we used the non-COPD specific Feeling Thermometer (FT, scores 0-100) as a valid and reliable instrument to measure HRQL. We ascertained the presence of comorbidities that may impact on HRQL through self-report and chart review. In the analysis, we included patients who had a FT ≥ 3 points (p<0.05 minimal important difference) in univariate analysis adjusted for FEV1.

Results: Coronary heart disease (p=0.018), diabetes (p=0.009), psychiatric disease (p=0.017) and urogenital disease (p=0.018) were most strongly associated with FT <67. ROC analysis with the non-COPD specific Feeling Thermometer (FT, scores 0-100) as a valid and reliable instrument to measure HRQL.

Conclusion: A simple index that counts the presence of four comorbidities can be used to quantify the impact of comorbidities in COPD patients in research and practice.

P3480 Prevalence of dyspepsia in COPD patients: Experience in a large Canadian cohort Gauthier Andréanne, Chalifoux Geneviève, Poirier Claude 1Integrated Care Unit, Hospital Clinic, Ciberes, IDIBAPS, Univ. Barcelona, Barcelona, Spain; 2Epidemiology Unit, PAMEM-IMIM, Barcelona, Barcelona, Spain

It has been shown that dyspepsia can be associated with COPD and in some cases closely linked to COPD exacerbations. The association of dyspepsia with COPD severity (FEV1, respiratory failure) and medications is not well described. The aim of this study is to evaluate the prevalence of dyspepsia in a large Canadian COPD cohort and to identify risk factors.

We retrospectively reviewed files of 1247 COPD patients. We classified patients as dyspepsia-positive (D+: 513 patients or 41%) or dyspepsia-negative (D-: 734 patients or 59%). Mean age was similar in D+ and D- (71.6 y/o versus 70.2) and we found no difference in FEV1 (44.97% versus 45.07%, p=0.05). Dyspepsia was more frequent in female patients (54.4% versus 45.4%, p<0.02) and in patients receiving home oxygen therapy (35.1% versus 26.8%, p<0.02). Active smoking was inversely related to dyspepsia (31.8% in D+ versus 41.0% in D-, p<0.001). Frequent acute exacerbations (>1/year) was also associated with dyspepsia (80.3% versus 71.7%, p<0.001). Finally, dyspepsia was positively related to cardiovascular and osteoporotic comorbidities (86.7% versus 68.4%, p<0.001). No relation was found with medications use, notably inhaled corticosteroids.

Conclusion: As reported by other publications, our retrospective study noted a high prevalence of dyspepsia in COPD patients and there was no relation with disease severity (expressed by the FEV1). Female sex, frequent acute exacerbations and comorbidities appear to be associated with dyspepsia. Surprisingly, we found a negative association with smoking status. Dyspepsia treatment consequences should now be addressed closely (QOL, exacerbations, FEV1 decline).

P3481 Three-year follow-up study of inflammatory markers in chronic obstructive pulmonary disease Renata Ferrari, Suzana Tanni, Laura Caram, Camila Corrêa, Corina Corrêa, Rosana Martin, Irma Godoy. Department of Internal Medicine, Botucatu Medical School - Sao Paulo State University - UNESP, Botucatu, Sao Paulo, Brazil

Studies show that values of Interleukin-6 (IL-6) and C-reactive protein (CRP) does not change significantly in COPD patients over one-year period. However, long-term studies of these mediators are lacking. We aimed to evaluate by high sensitivity ELISA (BioSource International Inc, Ca, USA) and C-reactive protein, CRP, in patients with COPD.

Results: Twenty-four COPD patients (16 males, 8 females) were included. Plasma concentration of Interleukin-6 had not change significantly during the follow-up period. However, tolerance exercise, dyspnea and BODE index worsened after three years. Plasma concentration of Interleukin-6 was measured by high sensitivity ELISA (BioSource International Inc, Ca, USA) and C-reactive protein.
P3482 A qualitative study of self-management in COPD: Attitudes and priorities of patients for making health behaviour changes

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Pivotal to successful chronic disease self-management is achieving adoption and maintenance of health behaviours that influence disease progression and impact.

Aim: To evaluate patients’ uptake and attitudes to health behaviour change in the Snail9 framework consisting of the items: smoking, nutrition, alcohol consumption, physical activity, psychosocial wellbeing and symptom management.

Methods: Community nurse mentors trained in a self-management approach, mentored 90 participants with COPD for up to 12 months by telephone. Participants’ views were sought during semi-structured interviews with a purposive representative sample. Data analysis by two independent authors used an Iterative Thematic approach. Health status was measured using SGRQ, HADS and MRC scales.

Results: In 20 participants (50% male, 50% current smokers) with COPD (GOLD stage: moderate 15, severe 5), mean age 65-4 years, the SGRQ overall score was 45 (SD 25.8). We found three groups related to health behaviour change attitudes. 8 (40%) subjects were actively making changes; 9 (45%) subjects were open to making changes and 3 (15%) subjects were more resistant. Severity of COPD and current smoking status were not major influences on attitude. Mentoring increased awareness of COPD effects and helped develop personal and behaviour change strategies, importantly even in those not actively making changes. Physical activity was most frequently targeted for changes. 50% of current smokers developed plans to target smoking. Motivation to maintain changes was increased by mentor support.

Conclusions: Health behaviour change in COPD at all stages can be supported by regular telephone mentoring.

P3483 Assessment of self-management needs among patients with COPD

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Introduction: While self-management is an essential part of chronic illness care, little is known about patients’ perspectives of their self-management needs.

Objective: To address this gap we conducted a cross-sectional, self-management needs assessment among patients with COPD.

Methods: Patients were enrolled from clinics as part of a self-management intervention trial. Patient activation was categorized based on their confidence in self-management and on motivation to participate in their care. Behavioral intentions addressed readiness to quit smoking and to meet physical activity goals.

S-efficacy was assessed using a COPD-specific scale. Open-ended questions addressed self-care facilitators, barriers, and goals.

Results: Of 76 patients enrolled, mean age was 69.2 years with 49.1% female. For patient activation 29.0% are active, 31.6% high effort, 23.7% compliant, and 15.8% passive. Among current smokers the majority are interested in quitting with 35% contemplation, 30% preparation, and 20% action. While mean levels of reported self-efficacy were similar across domains, the proportion reporting low levels of confidence were greatest for physical activity and behavioral domains (56.6%). In a qualitative analysis of 34 interviews major themes relevant to self-management facilitators, barriers, and goals were fear (i.e., disease progression, suffocation/death), loss (i.e., functioning, independence), cherished activities), co-morbid limitations, stigma/social isolation, and desire for change (i.e., improve functioning, better care, information, understanding).

Conclusions: The results from this cross-sectional analysis highlight the complexity of self-management needs among patients with COPD.

P3484 The views and attitudes of patients, carers and healthcare professionals on nutrition in COPD

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Introduction: Weight loss is a reversible prognostic factor in COPD but there is little evidence on effective community nutritional intervention for underweight COPD patients. This study is part of a feasibility study on designing and evaluating such nutritional intervention.

Aims: To find out the views and attitudes of patients, carers and healthcare professionals (HCPs) towards nutrition in COPD and to gain insight on:

1. Effect of weight loss
2. Factors influencing eating
3. Dietary counselling
4. Current COPD nutritional pathway

Methods: Six underweight COPD patients, 6 carers and 8 HCPs were recruited by purposive sampling and formed 3 semi-structured focus groups. Discussions were recorded and transcribed verbatim, sorted with NVivo software and analysed using framework qualitative analysis.

Results: Weight loss was important not only for health but also for cosmetic, psychological and financial reasons.

Patients chose food according to taste, cost, consistency, chewability and availability. They tolerated only small portions but valued variety and ate more when in company. Oral nutritional supplements (ONS) were disliked but some found it useful as an energy source when ill.

Dietetic consultations were perceived as useful if individualised and regular.

Negative views on underweight in COPD led to delayed dietetic referrals. Screening for underweight and weight loss was recommended.

Conclusions: To increase adherence to the nutritional programme, varied high-calorie foods which are easily available, cheap and affordable should be considered.

The nutrition support intervention should involve food fortification, snack and/or ONS and incorporate individualised consultation.

P3485 Muscle regrowth in COPD patients induced by anabolic steroids is amplified by systemic glucocorticoids (GC): A potentiating interaction between GC and IGF-1

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Muscle wasting is associated with poor prognosis in COPD. Anabolic steroids can induce muscle regrowth and stimulate muscle insulin growth factor 1 (IGF-1) signaling, while high dose systemic glucocorticoids (GC) can induce muscle atrophy. The current study aimed to gain insight into the combined effect of GC and anabolic stimulation on muscle. Post-hoc analysis of a previously published clinical trial (Creeberg, et al. Chest 2003; 124:173–181) investigating m-drolone decanoate (ND) efficacy on male COPD patients revealed that gain in fat free mass (assessed by deuterium dilution), was highest in ND/GC 22.5±5.7 11W (p<0.05) vs ND/no-GC 8.54±4.08W (NS) compared to their respective controls placebo/GC and placebo/no-GC. Muscle function determined by peak workload similarly increased most in the ND/GC group 22.5±5.7 11W (p<0.05) vs ND/no-GC 8.54±4.08W (NS) compared to their respective controls. During muscle regrowth activated satellite cells (myoblasts), differentiate and fuse with myofibers, which is stimulated by IGF-1. In cultured C2C12 myoblasts, GC strongly impaired (>2-fold) and IGF-1 stimulated (>2.5-fold) multiple parameters of muscle differentiation, like Creatine Kinase activity, muscle contractile protein content and myoblast fusion. However when combined, a synergistic stimulation (>3-fold) of myogenic differentiation parameters was observed, which is in line with our clinical data. Unraveling the potentiating interaction between GC and IGF-1 may provide new leads to enhance efficacy of intervention strategies to prevent or restore muscle wasting in COPD.

P3486 The effects of nutritional support with omega-3 rich diets on respiratory functions, exercise capacity and quality of life in stable COPD

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Objective: To determine the effects of nutritional support with omega-3 rich diets on respiratory functions, exercise capacity and quality of life in COPD patients.

Methods: The study was planned on 21 stable COPD patients. A questionnaire...
was applied to patients including demographic and disease information, food-
frequency, a three-d 24-h dietary record and Subjective Global Assessment. SF-36,
6 Minute Walking Test, BORG scale and spirometric tests were performed to the
patients. Before the personal diets were planned, patients' personal needs were
determined and an omega-3 rich diet was administered with an omega-3 dietary
supplementation (180 mg EPA and 120 mg DHA).

Results: After dietary intervention, patients' mean BORG scale result was de-
creased (p<0.05). After diet, physical component score and mental component
score were increased and these differences between before and after intervention
were statistically significant (p<0.05). The mean walking distance of the patients
was 395.9±53.65 m before intervention and 420.8±48.07 m after intervention
(p<0.05). Before dietary intervention, FEV1/FVC was 64.1±11.61% and after
the intervention this ratio increased to 67.8±9.37% (p<0.05). After diet, there
was a significant negative correlation between dietary omega-3 and BORG scale
(r=-0.623, p=0.003), a significant positive correlation between dietary omega-3
and SF-36 Physical Health component (r=0.456, p=9.038).

Conclusion: While planning the COPD patients' diet it should be so important to
provide adequate energy, low carbohydrate and high omega-3 content within diets
during the lifetime of survival.

P3487

Association of weight loss in COPD patients with low body mass index on
outcomes
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The impact of COPD phenotypes based on body composition and it's change
was evaluated on longitudinal outcomes in COPD patients from the "Evaluation
of COPD Longitudinally to Identify Predictive Surrogate Endpoints" (ECLISEP
study). The assessment of the body mass index (BMI) was done at Year 1 for 364 COPD patients and assessed the impact of BMI and the change in
BMI from baseline to year 1 on mortality during the subsequent two years of the
study. During the follow-up, there were 31 deaths. Using logistic regression, each
decrease from baseline to Year 1 to 1 kg/m² in BMI in this underweight group
was associated with a 51% increased risk of death after controlling for FEV1%
predicted and BMI.

Logistic Regression with mortality during Year 2 and Year 3 as dependent variable in underweight subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inc</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI change, Br. to Y1</td>
<td>-1 kg/m²</td>
<td>1.51</td>
<td>(1.11, 2.05)</td>
<td>0.008</td>
</tr>
<tr>
<td>FEV1 % predicted, Y1</td>
<td>1% pred</td>
<td>1.08</td>
<td>(0.95, 1.24)</td>
<td>0.237</td>
</tr>
<tr>
<td>BMI at Y1</td>
<td>-1 kg/m²</td>
<td>1.09</td>
<td>(0.91, 1.30)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

These findings suggest that for a group of underweight COPD patients, the magn-
itude of weight change in the previous year is an independent predictor of poor
outcome.

Funded by GlaxoSmithKline (SCO104960, NCT00292552).

P3488

Hypoxia altitude simulation test (HAST): Arterial blood gases or pulse oxim-
etry? 

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Background: Supplemental oxygen is recommended when PaO2 is expected to
fall below 6.6 kPa during air travel. Hypoxia altitude simulation test (HAST)
with monitoring of arterial blood gases (ABG) is the most frequently used test
to identify those at risk of developing in-flight hypoxemia. If pulse oximetry can be
used as a substitute for ABG, HAST would be simpler to perform and thereby
more available.

Aim: We hypothesised that pulse oximetry may replace ABG when using HAST
in the pre-flight evaluation of COPD patients.

Methods: COPD patients referred to HAST were consecutively included. HAST
was performed with arterial blood gases taken from an arterial line in addition
to continuous measurement of SpO2 with a pulse oximeter. After 15 min with
inhalation of a hypoxic gas (15% O2, equivalent to 2348 m above sea level),
PaO2 and SpO2 were simultaneously registered.

Results: 100 COPD patients (42% men) were included, mean (SD) age 65 (8)
years, FEV1: 41 (33)% predicted. SpO2 baseline was 93 (3)% PaO2: HAST 6.3
(0.6) kPa, and SpO2: HAST 83 (4)%. There was a strong correlation between PaO2
and SpO2: HAST (r=0.81, p<0.001). A ROC analysis showed strong prog-
nostic properties (area under curve 0.928) for use of pulse oximetry for detection
of in-flight PaO2 < 6.6 kPa. The suggested cut-off value for PaO2 < 6.6 kPa was
SpO2: HAST < 85% (sensitivity 89%, specificity 81%).

Conclusions: Pulse oximetry may replace arterial blood gases during HAST. A
SpO2 < 85% can predict development of severe in-flight hypoxemia (PaO2 < 6.6
kPa) with a sensitivity of 89% and a specificity of 81%. Use of SpO2 during HAST
will simplify the test considerably.

P3489

Ambulatory care of patients with bronchial asthma participating in a
German disease management program

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Central Research Institute for Ambulatory Health Care in Germany; Cologne,
Germany

Background: In 2006 a disease management program for bronchial asthma
was started in the North Rhine region, Germany, focusing on patient education
and optimisation of quality of care.

Methods: By the end of 2009 data from 55,928 adults (A) and 13,021 children
(C, aged 5 to 17 years) are analysed cross-sectionally. Between 2007 and 2009
continuously documented patients are analysed longitudinally. Standardised medi-
cal records provide information of symptom frequency, non-medical interventions
and pharmacotherapeutics.

Results: In 2009 35% of the adults suffer at least from weekly symptoms (C 13%),
in 38% symptoms are documented less than once per week (C 50%). Control of
inhalation techniques is conducted for 72% of all adults (C 79%) and 63% are
provided with a self-management plan (C 86%). Asthma education is advised to
47% of all patients (C 65%), but only 40% of these subsequently participate in
such an education (C 48%). Most common pharmacotherapy in patients with at
least weekly symptoms consists of short-acting beta-agonists (SABA) as reliever
medication (A 70%, C 82%), inhaled corticosteroids (ICS) (A 71%, C 72%)
or long-acting beta-agonists (LABA) as controller medication (A 63%, C 54%)
SABA (2007-09 A: 69-68%, C: 91-92%), LABA (A: 56-60%, C: 26-22%)
and ICS in adults (70-68%) are prescribed rather constantly over time, prescription
rates of ICS in children decline (73-58%).

Conclusions: Prescription rates of SABA, LABA and ICS seem to be in accor-
dance to recommendations by asthma guidelines. Control of inhalation devices
is at a high level, but rate of participation in patient education needs further
improvement. Limitations due to potential selection bias have to be considered.

388. Insight into mechanisms of respiratory infections

P3490

LSC 2011 Abstract: The role of IL-25 in rhinovirus-induced asthma
exacerbations

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Rhinoviruses (RV) are the major causative factor of asthma exacerbations (AE).
While RV-mediated inflammation is implicated in asthma, it is unknown how the
immune response to RV infection interacts with Th2 immunity causing an AE.
Epithelial-derived IL-25 is an important regulator of Th2 immunity and plays a
role in asthma pathogenesis. We hypothesised that RV infection of the epithelium
induces IL-25 production facilitating immunopathogenesis of AE. We measured
IL-25 mRNA in mouse models of RV infection and RV-induced exacerbation
of allergic airway inflammation [1]. In vitro IL-25 gene induction was also assessed
in asthmatic and normal bronchial epithelial cells (BEC) infected with RV and
stimulated with IL-4. In vivo and in vitro results demonstrated that RV induced
IL-25 mRNA as measured by qPCR. Airway challenge with ovalbumin (OVA) fol-
lowed by RV infection in sensitised mice exacerbated allergic airway inflammation
and coincided with enhanced IL-25 mRNA expression compared with allergen
or infection alone. Similarly, RV and IL-4 treatment of BECs resulted in the
highest levels of IL-25 mRNA. The novel finding that RV infection induces IL-25
represents a link between antiviral responses and Th2 inflammation identifying a
role for IL-25 in RV-induced AE. Allergen/IL-4 treatment enhanced RV-dependent
IL-25 expression thus a Th2 environment and virus may result in exacerbated Th2
inflammation mediated by IL-25.

Reference:
1 Bartlett, N.W., et al. Mouse models of rhinovirus-induced disease and exacer-

P3491

Pulmonary viral infection in hematologic patients with and without stemcell
transplantation

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Michael Tamm 3, 1 Clinic of Pulmonary Medicine and Respiratory Cell Research,
University Hospital Basel, Basel, Switzerland; 2 Clinic of Hematology, University

621s

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Pulmonary complications are frequent in hematologic patients. Regular investigation of BAL fluid includes bacterial/fungal culture, staining and PCR for mycobacteria, immunohistochemistry/Grocott staining for pneumocystis and cell differentiation. The increasing use of PCR to search for different viruses is demonstrated. In this study we analysed the diagnostic yield of a recently established multi-PCR for detection of 13 viruses. 219 hematologic patients underwent bronchoscopy with BAL from September 2009 to January 2011. 28 of patients received high dose chemotherapy, 143 underwent autologous and 13 allogeneous stem cell transplantation. Bacteria were cultured from 43 (20%) BALs: staphylococcus aureus, pseudomonas aeruginosa, streptococcus pneumoniae, enterococcus, moraxella, enterobacteriaceae, klebsiella, corynebacterium, mycoplasma pneumoniae, mycoplasma hominis, chlamydia pneumonae, bordetella pertussis. There were 7 cases of pneumocytus. In two patients we found mycobacterium gordonae. Aspergillus was cultured in 4 cases. In 81 (37%) patients viruses were documented. Most often we found rhinovirus (n=31; 14%), followed by CMV (n=18; 8%), HSV (n=13; 6%), RSV (n=10; 4.5%), coronaviruses (n=8; 3.6%), adenovirus (n=7; 2.5%), parainfluenza- and metapneumovirus (each n=5; 2.2%), H1N1 (n=1; 1.8%), influenza (n=3; 1.4%), and HHV6 (n=1; 0.4%).

Summary and conclusion: The incidence of viral infections is very high in patients with hematologic diseases and pulmonary symptoms. Multiplex PCR in the BAL should be introduced as a routine diagnostic procedure in this patient group allowing to withdraw or avoid antibiotic or antifungal therapy in many cases.

P3492 Impaired innate immunity to rhinovirus in severe asthmatic children

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The pathogenic mechanisms of rhinovirus-induced asthma exacerbations are incompletely understood. Impaired production of innate IFN-β and IFN-λ have been identified in bronchial epithelial cells and bronchoalveolar lavage macrophages from atopic mild moderate asthmatics upon rhinovirus infection in vitro. These cells display similar production of pro-inflammatory cytokines when compared to cells cultured from non-asthmatic, non-atopic individuals, and are observable in asthmatic patients. In the present study, bronchial epithelial cells were cultured from severe asthmatic children (n=8, mean age 11yr, range 9-15, 63% male) and non-asthmatic non-asthmatic controls (n=10, mean age 7yr, range 6-15, 70% male). Cells were infected with RV1B, RV16, or medium and mRNA, protein and virus release was measured at 8-48h post infection. Cells from severe asthmatic children displayed significantly reduced IFN-β (p<0.05) IFN-λ-1 (p<0.05) and IFN-λ-2/3 mRNA (p<0.05), but not IL-8 (p>0.05) or ENA-78 (p>0.05) compared to controls. Cells cultured from severe asthmatics had significantly higher RV1B (p<0.01). RV16 (p<0.05) release at 48h, compared to controls. Impaired RV1B induced IFN-β and IFN-λ-2/3 also showed strong negative correlations with increased virus load (r=-0.79, p=0.013 and r=-0.65, p=0.013 respectively). RV1B induced IFN-λ-2/3 from severe asthmatics also showed strong negative correlations with total serum IgE (r=-0.75, p=0.04) and a trend for a negative correlation with total serum IgE (r=-0.75, p=0.04). These findings suggest that there is a significant role for RV1B and RV16 in the pathogenesis of asthma exacerbations in severe asthmatic children.

P3493 Tyrosine sulfation in the N-terminal domain of human C5aR is necessary for high-afﬁnity binding of chemotaxis inhibitory protein of staphylococcus aureus

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Background: Staphylococcus aureus evades host defense through releasing several virulence proteins, such as chemotaxis inhibitory protein of staphylococcus aureus (CHIPS). Previous studies have shown that extracellular N terminus of C5a receptor (C5aR) forms the binding domain for CHIPS. Tyrosine sulfonation is emerging as a key factor in determining protein-protein interaction. The goal of this study was to evaluate the role of tyrosine sulfation of N-terminal C5aR in binding to CHIPS.

Methods: Expression plasmids encoding C5aR and its mutants were made by PCR and site-directed mutagenesis. HEK 293T cells were transfected with plasmids encoding C5aR using calcium phosphate. Reconstituted CHIPS protein was purified. Western blotting was used to assay the binding of CHIPS to C5aR or its mutants and p-38 phosphorylation.

Results: We report that CHIPS exclusively binds to C5aR, but not to C5L2 or C5L1. A nonspeciﬁc sulfation inhibitor, sodium chloride, diminishes the binding ability of C5aR to CHIPS. Blocking sulfation by mutation of tyrosine to phenylalanine at positions 11 and 14 of C5aR N terminus completely abrogates CHIPS binding. When tyrosine 14 alone was mutated to phenylalanine, the binding afﬁnity of recombinant CHIPS was substantially decreased. CHIPS fails to induce p-38 phosphorylation in cells overexpressing wild-type C5aR or its mutants.

Conclusion: This study deﬁnes a structural basis of C5aR-CHIPS association, in which tyrosine sulfation of N-terminal C5aR plays an important role in CHIPS binding. Our data would make it possible to develop potent drugs for therapeutic intervention.

P3494 shRNAs signiﬁcantly reduce the replication of RSV in vitro

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Background: RNA interference (RNAi) is a powerful tool to silence gene expression on the level of mRNA. To knock-down gene expression by using RNAi two major methods of mRNA silencing exist. First method utilizes siRNA (small interfering RNA), a readily processed dsRNA, that enters RISC complex and degrades the target mRNA after transcription into the cells. The second method based on the construction of plasmid DNA that expresses shRNA (short hairpin RNA) from U6 or CMV promoter. shRNA gets processed by Drosha and Dicer RNAses inside the cell before it translocates to the cell cytoplasm and affects the level of target mRNA. In this study we investigated the ability of specific vector constructs coding shRNA molecules to target the expression of respiratory syncytial virus (RSV) phosphoprotein in vitro and thus inhibit the replication of RSV.

Methods: Lentiviral vector pGIPZ expressing GIPZ-IRE5-shRNA/Amica30 casette was modified by introducing BamHI restriction site downstream of the original recombinant.

Results: Three shRNAs against phosphoprotein P RSV and shRNA against human CD43 as a control were generated and cloned into modified so-called pGIPZ vector. Monkey kidney cells MA-104 were stably transfected with four shRNA constructs. MA-104 cells transfected with shRNA constructs against RSV P protein demonstrated significant inhibition of RSV replication after the infection than compared to the control and not transfected cells.

Conclusion: The generated constructs can be successfully used for efficient gene silencing and virus replication inhibition in vitro.

P3495 Novel narrow spectrum kinase inhibitors inhibit rhinovirus replication via enhancement of interferon expression in nasal epithelial cells of atopic and non-atopic patients

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RATIONAL. Rhinovirus infection is one of important causes of asthma exacerbation. Deficient innate immune response was reported in asthma accounting for increased susceptibility of asthmatic patients to respiratory viral infections. The aim of this study was to evaluate the effects of RSV568 and RSV1088, narrow spectrum kinase inhibitors (NSKis), on HRV16 replication and interferon expression in nasal brushing epithelial cells (NBEC) from atopic (A) and non-atopic (NA) patients.

Methods: NBECs were infected from 9 A- and 9 NA-rhinitis patients. Cells were treated with RV568, RV1088, fluticasone propionate (FP) or tiotropium bromide (TB), and infected with HRV16 (5MOI). After 1 hr absorption, cells were washed with PBS and then treated with compounds again. After 8 hours, cells were collected to determine viral RNA and IFN-λ, IFN-β mRNAs by real time RT-PCR.

Results: HRV16 viral load (copy number) was 9 fold higher in NBECs of A-patients than those of NA-patients (48.6±10 and 5±4 respectively, p=0.083). In addition, IFN-λ expression was significantly lower in A-patients than NA-patients (copy number, 80±1.22, 136±3.174, p=0.02). IFN-β expression showed similar trends. Both RV568 (100nM) and RV1088 (10, 100nM) inhibited HRV16 replication, and significantly increased IFN-λ, β expression, particularly in A-patients. FP (100nM) and TB (100nM) did not inhibit viral load or increase IFN expression.

Conclusions: HRV16 infection is more severe in NBECs of A- compared to NA-patients due to deficient HRV16-induced IFN expression, that is restored by RV568 and RV1088.

P3496 Cigarette smoke extract increases the adhesion receptor for S. pneumoniae in vitro

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Background: Although the mechanism is unknown, cigarette smoke exposure increases the risk of pneumococcal infections in humans. We have recently shown that fossil fuel derived particulate matter increases adhesion of S. pneumoniae to epithelial cells (NBEC) from atopic and non-atopic patients.
via upregulation of platelet activating factor receptor (PAFr) expression on airway cells. We therefore aimed to assess whether cigarette smoke extract (CSE) upregulates the PAFr expression in vitro.

**Methods:** The human lung epithelial (A549) cell line was incubated with very low concentrations of CSE (0.01%, 0.02% and 0.05%) for 4 hr. PAFr expression, adjusted for non-specific staining, was then assessed by flow cytometry using a PAFr human monoclonal antibody.

**Results:** CSE stimulated dose-dependent increase in PAFr expression, with an increase in mean PAFr fluorescence and % positivity (Figure 1 and Table 1).

**FACS analysis showing dose (%) of CSE vs mean fluorescence**

<table>
<thead>
<tr>
<th>Dose (CSE)</th>
<th>% Positivity</th>
<th>Mean Fluorescence (isotype subtracted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95</td>
<td>21</td>
</tr>
<tr>
<td>0.1</td>
<td>95.4</td>
<td>332</td>
</tr>
<tr>
<td>0.2</td>
<td>96.1</td>
<td>432</td>
</tr>
<tr>
<td>0.5</td>
<td>96.3</td>
<td>735</td>
</tr>
</tbody>
</table>

**Conclusion:** CSE stimulates PAFr, the receptor for S. pneumoniae adhesion to lower airway cells, and may be the mechanisms underlying the epidemiological association between active and passive cigarette exposure and invasive pneumococcal disease in adults and children.

**FACs analysis showing a dose response relationship between CSE and PAFr expression.**

**P3497**

**Assessment of tracheal tube biofilm translocation during mechanical ventilation and lung injury**

Gianluigi Li Bassi1, Laia Fernández-Baral1, Joan Daniel Martí1, Montserrat Rigol1, Laura Muñoz1, Miquel Ferrer1, Jordi Vila1, Francesco Basile1, Antoni Torres1, Thoras Clinic Institute, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain; 2Pneumology Department, Thoras Clinic Institute, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain; 3Cardiology Department, Hospital Clinic, CRESIB, Barcelona, Spain; 4Microbiology Department, Hospital Clinic, CRESIB, Barcelona, Spain; 5Cardiology Service, Thoras Clinic Institute, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain

**Introduction:** The role of bacterial biofilm, within the endotracheal tube (ETT), in the pathogenesis of respiratory infections is still under debate.

**Objectives:** To study effects of length of stay under mechanical ventilation (MV) on bacterial biofilm translocation from within the ETT into health and injured lungs.

**Methods:** ETTs colonized by biofilm were obtained from an associated study where pigs underwent oropharyngeal bacterial challenge by Pseudomonas aeruginosa (PA) and 72h MV. Those ETTs were used in 8 healthy pigs (32.1 ± 2.5 kg) on MV (Vt: 8 ml/kg, RR adjusted based on pH, 7.2 ± 0.25). Pigs were randomized into 4 groups (2 pigs/group) to be MV up to 24h (Group1), 48h (Group2), 72h (Group3) and 48h with lung injury caused by oleic acid (OA) (Group4). Upon extubation, 4 samples from trachea and main bronchi and 7 from segmental bronchi were excised for PA quantification.

**Results:** In pigs of group 3, 1 hour after OA instillation, PaO2/FiO2 decreased to 199 ± 127. Upon extubation, ETT PA colonization was 5.7 ± 1.6, 6.4 ± 0.5, 7.6 ± 0.5 and 7.6 ± 0.6 log cfu/mL in groups 1-4, respectively (p = 0.21). As depicted in figure 1, the airway tissue/ETT PA colonization ratio of trachea and main bronchi was 0.59 ± 0.37. Colonization of segmental bronchus was infrequent.

**Conclusion:** Bacteria from within the ETT PA biofilm rapidly translocate up to the main bronchi, however, distant colonization is uncommon even when lungs are injured.

**Figure 1**

**Conclusions:** From within the ETT PA biofilm rapidly translocate up to the main bronchi, however distant colonization is uncommon even when lungs are injured.

**P3498**

**Detection of linezolid in endotracheal tube biofilm of ventilated pigs with methicillin-resistant Staphylococcus aureus (MRSA) pneumonia**

Laia Fernández-Baral1, Miquel Ferrer1, Laura Guerrero2, Delors Soy2, Jordi Vila1, Gianluigi Li Bassi1, Josep Maria Sierra4, Lina Maria Saucedo2, Pilar Martínez-Olondriz1, Montserrat Rigol1, Mariano Esperatti1, Néstor Luque1, Joan Daniel Martí1, Antoni Torres1, Pneumology Department, Thoras Clinic Institute, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain; 2Pharmacy Service, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain; 3Microbiology Department, Hospital Clinic, CRESIB, Barcelona, Spain; 4Microbiology Department, Hospital de Bellvitge, Barcelona, Spain; 5Cardiology Service, Thoras Clinic Institute, Hospital Clinic-IDIBAPS, Ciberes, Barcelona, Spain

**Introduction:** Linezolid presents good penetration into respiratory secretions; we hypothesized that secretions could transport linezolid into ETT and limit burden of MRSA in biofilm.

**Aim:** To determine linezolid concentration in biofilm inside the ETT using High-performance liquid chromatography (HPLC).

**Methods:** We analyzed 16 samples of ETT from pigs with MRSA pneumonia, ventilated up to 96 hours and treated with linezolid (10 mg/kg every 12h IV). To determine linezolid concentration by HPLC we disrupted the biofilm matrix with several sonications, enzymes and perchloric acid. We also assessed MRSA count in each ETT sample.

**Results:** We retrieved from the ETT samples 63.4±54 mg of biofilm. In 4 (25%) samples linezolid was inferior to the sensitivity of the technique (1.56 μg/mL). In the remaining 12 samples the concentration of linezolid was 38 (11-83) μg/mL of biofilm (median (IQR)). Hence, linezolid concentration in biofilm was 19 (5-41) times above the MRSA MIC for linezolid (2 μg/mL). The concentration of MRSA in the biofilm of pigs treated with linezolid was 1.98±0.84 Log CFU/mL. No significant correlation was found between biofilm concentration of linezolid and MRSA burden (r=0.48, p=0.11).

**Conclusion:** Despite the high concentration of linezolid above the MIC in biofilm inside the ETT, MRSA was found in most samples of pigs treated with this antibiotic, without significant correlation between linezolid levels and MRSA burden.

**Funded:** FIS 05/0620, 070419, 016077 and 050136, SEPAR 2005, Fundación Lilly, Ciberes (CB06/06/0028), 2009-SGR-911, IDIBAPS, FUCAP 2010.

**P3499**

**Moderate aerobic exercise training attenuates inflammatory response to Streptococcus pneumoniae in mice**

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**Streptococcus pneumoniae** is one of the most important causes of morbidity and mortality in respiratory diseases. Aerobic exercise is known to attenuate inflammatory processes in some lung injuries.

**Objectives:** To study if moderate exercise training prior to bacterial infection alters the pulmonary inflammatory profile.
Methods: 40 Balb/C mice (14-16 weeks) were divided into 4 groups: Control (C), Aerobic Exercise (AE), S. pneumoniae infection (P), S. pneumoniae + Aerobic Exercise (P+AE). Moderate intensity treadmill training was performed over 4 weeks, 5 times/wk, 60 min/session in the AE and P+AE groups. After 72 hs of the last exercise training session, P and P+AE groups were challenged intranasally with pneumococcal strains M10 (type 11A) through the inoculation of 50 μl of the suspension of the bacteria in 0.9% saline. C group did not receive intranasal instillation or exercise training. Bronchoalveolar lavage (BAL) was performed 10 days after the intranasal challenge to quantify the number of total cells, macrophages, neutrophils and lymphocytes.

Results: S. pneumoniae inoculation resulted in increase number of total cells (18.63 ± 10^5 cels/mL ± 9.02; p < 0.001), macrophages (6.49 ± 10^5 cels/mL ± 1.94; p < 0.001) and neutrophils (8.19 ± 10^5 cels/mL ± 6.84; p < 0.001) while moderate exercise training in S. pneumoniae inoculated animals resulted in significantly decreased total number of cells (10.15 ± 10^5 cels/mL ± 1.10; p < 0.001) and neutrophils (1.53 ± 10^5 cels/mL ± 0.84; p < 0.000) in BAL.

Conclusion: These results suggest that moderate aerobic exercise training attenuated the neutrophilic inflammation in an animal model of bacterial infection supported by FAPESP, LIMHC-FMUSP, CNPq, Brazil.

P3500
Different modes of allergen – Rhinovirus interaction control chemokine production
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Interacting immune responses to rhinovirus (RV) and allergen in asthma are thought to increase the risk of asthma exacerbations. To investigate this we used a mouse model of RV-induced asthma exacerbation and assessed expression of chemokines in Th1 and Th2 recruiting chemokine protein in BAL fluid. Experimental groups: allergen (OVA)-challenged, RV-infected (RV-OVA); OVA challenged, mock infected with UV-inactivated U-V(OVA); RV-infected mock allergen challenged with PBS (RV-PBS) and double negative control (UV-PBS).

Results: CCL11 and CCL24 (eotaxin 1 and 2) in RV-OVA were significantly increased (P < 0.001) vs UV-OVA. RV infection alone did not induce either eotaxin but synergistically augmented eotaxin production in allergic mice. For Th1 chemokines CXCL11 (I-TAC) and CCL5 (RANTES) the opposite was true. RV infection drove eotaxin and was synergistically increased by allergen (OVA) compared to RV-PBS for CCL11 (P = 0.001) and CCL5 (P < 0.01). Next we examined Th2 cell recruiting chemokines CCL17 (TARC) and CCL22 (MDC). Both OVA- and RV-alone stimulated increased expression (UV-OVA and RV-PBS P < 0.001 compared to UV-PBS) and increased levels observed in RV-OVA (P < 0.05 and P < 0.001 for UV-OVA and RV-PBS respectively) were consistent with an additive interaction between OVA and RV. Associated with increased chemokine production we observed greater lung recruitment of activated (CD69+) CD4+ T cells (P < 0.01) compared to UV-OVA and expression of IL-5 and IL-13. Thus for the chemokines investigated we observed 3 different modes of allergen-virus interaction 1) allergen-induced, augmented by virus, 2) virus-induced, augmented by allergen, 3) allergen and virus additive.

P3501
An anti-human ICAM-1 antibody inhibits human rhinovirus infection in the mouse model of human major group rhinovirus infection
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Background: Antimicrobial peptides (AMPs) as such as Secretory Leukocyte Protease Inhibitor (SLPI) and Elafin are important component of host innate immune response to prevent against infection of mucosal surfaces. Their role in bacterial infection is well described but little is known regarding their role in respiratory viral infections.

Aims: We investigated the effects of rhinovirus infection on production of SLPI and elafin by monocyte derived macrophages (MDM).

Methods: MDM derived from healthy donors were infected with rhinovirus-16 (RV16). Cells and supernatants were harvested and SLPI and elafin mRNA and protein were measured by qPCR and ELISA respectively.

Results: Compared to cells infected with UV-inactivated virus RV16 induced expression of SLPI mRNA (11.7-fold induction, P = 0.005) and protein (53.0±4.5±76pg/mL vs. 95.2±3.2±63,P = 0.014) in MDM at 24 hours.

Figure 1
There was a trend towards upregulation of elafin at 48 hours for both mRNA (2.17-fold induction, P = 0.055) and protein (13.3±3.3±13.37pg/mL vs 107.8±7.35.47,P = 0.14) but this was not statistically significant.

Conclusions: Rhinovirus infection of MDM upregulates production of SLPI and elafin and this is dependent on virus replication. These molecules may play an important role in the host defence response to respiratory virus infections.

P3503
Potential synergy of drugs with anti-viral and pulmonary oedema clearance activity may be advantageous for influenza patients
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Definition: Influenza is a serious public health problem that causes severe illnesses and deaths for Hospitalized patients and healthy people. A lot of patients needed medical treatment and many die from the disease every year. 30% of hospitalised patients with Influenza infection require intensive care and despite medical treatment 10% die. The most common cause of death is viral pneumonia and ARDS. Antiviral drugs like oseltamivir and zanamivir block increase and spreading of the virus in the body. Already existing virus particles will not be affected. In case of complications, 2/3 of patients show infiltrates on chest radiographs, giving strong evidence for ARF and pulmonary oedema which can deteriorate to ALIARDS. However, it has been shown that the AP301 peptide, representing the TIP domain of TNFs, has alveolar liquid clearance activity. It was proposed that a combination of anti-viral and anti-oedema substances would act synergistically. This was assessed in mice having been sublethally infected with Influenza strain A/PR8/34 per nasal. On day of infection, mice were treated with oseltamivir. AP301 peptide was applied intratracheally on days 0, 2 and 4 post infection. On day 9 post infection the effect on wet-dry weight ratio and pulmonary microvascular permeability was assessed. AP301 peptide alone had a beneficial effect compared to untreated mice. The additive effect of the combination of AP301/ oseltamivir combination was greater for reduction of lung oedema, which was in the range of control-treated but untreated mice. In conclusion, these preliminary experiments suggest a benefit of combining anti-viral drugs and substances with alveolar liquid clearing activity.
Acute exacerbations of COPD are mainly mediated by respiratory viruses or bacteria like non-typeable Haemophilus influenzae (NTHi) and Chlamydia pneumoniae (Cpn). To elucidate the interaction of viral/atypical pathogens and NTHi in respiratory diseases and human lung tissue with the TLR3 agonist Poly(I:C) as a model of viral infection and Cpn as an atypical, TLR2-inducing agent. Alveolar Epithelial Cells (AEC) and human lung tissue (HLT) were pre-incubated with Poly(I:C) or Cpn (strain CWS-029) and costimulated with NTHi 10^6 cfu/mL (strain Rd K320). After 24 hrs and supernatants were harvested for ELISA and Western Blot analysis and tissue was used for in situ-Hybridisation (ISH).

NTHi led to significant induction of Interleukin-8 (IL-8) production (HLT: Med 134848±22834 µg/mL vs. NTHi 341926±4390 µg/mL, n=12, p<0.001). NTHi and Poly(I:C) increased IL-8 production and had significant costimulatory effects as well as Cpn/NTHi-coinfection (AEC: NTHi+Poly(I:C) 18.48±1.93 µg/mL vs. NTHi 8.70±2.22 µg/mL, p<0.05, n=4; HLT: Cpn 199395±32822 µg/mL vs. Cpn+NTHi 367777±53895 µg/mL, p<0.05, n=6). TLR2- and TLR3-stimulation were mediated via MAP-kinas. ISH showed increased IL-8 and TLR2-expression in HLT in Cpn/NTHi-coinfection. Blocking TLR2 with a specific antibody led to partial reduction of IL-8 expression. These data indicate that TLR2- and TLR3-stimulation are necessary for inflammatory responses in NTHi-infection and that TLR-signaling might be important for enhanced inflammation in viral/NTHi and atypical/NTHi confections.

**Aim:** To define the role of γδ T cells in RV-induced asthma exacerbations using a mouse model.

**Methods:** The mouse RV-induced asthma exacerbation model comprised sensitisation and challenge of BALb/c mice with ovalbumin and infection with RV1B (RV-OVA) or UV-inactivated RV1B control (UV-OVA) concomitant with final allergen challenge. γδ T cells were depleted by intraperitoneal injection of anti-γδTCR antibody.

**Results:** RV infection increased total and activated lung γδ T cell numbers in the airways of atopic asthmatics following RV infection and that greater bronchoalveolar lavage (BAL) γδ T cell numbers were associated with greater airway hyperresponsiveness (AHR) and obstruction.

**Aim:** To investigate the expression of PAR in the airways of normal lung function smokers (NS) in vivo.

**Methods:** Endobronchial biopsies from 16 NS and 11 normal controls (NC) were stained for anti-PAR monoclonal antibody. PAR expression was assessed as percentage of epithelium stained for PAR over total basement membrane length by using computer-assisted image analysis.

**Conclusions:** This is the first description of in-vivo expression of PAR in the epithelium of NS compared to NC. Our data suggest that enhanced PAR expression may be the mechanism of increased vulnerability of smokers to pneumococcal infection.

**389. Phenotyping and monitoring of airway diseases**
the following parameters on FEV1 drop was also checked: age, sex, respiratory difficulties (dyspnoea, irritating cough, wheezing and allergic rhinitis symptoms), atopy, past medical history (PMH) of respiratory infection, smoking, chronic bronchitis. A 30% or higher FEV1 drop at bronchoprovocant dosages or concentrations lower than the planned cumulative dose or a 40% or higher FEV1 drop after inhalation of the whole bronchoprovocant dose was considered as severe.

Results: FEV1 drop was found in 248 persons (18%), of which 201 patients (14.6%) were finally diagnosed with BA (52 patients with OA, 149 with non OA origin). Statistically significant FEV1 drop was found in both subgroups among patients with a PMH of whirling, among patients with atopy and smokers.

Conclusion: Caution is recommended when performing BPC in some patients, particularly in those with suspected asthma who are smokers, diagnosed with atopy and those with a PMH of wheezing. These patients may experience greater discomfort from bronchial obstruction and therefore, the provocalive dose may need to be increased at a slower rate.

P3511 Gastro-oesophageal reflux disease, upper gastro-intestinal motility and autonomic function in adult asthmatics
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Introduction: Asthmatics have increased prevalence of gastro-oesophageal reflux disease (GORD). Oesophageal hypomotility, delayed gastric emptying (GE) and autonomic hypofunction increase GOR. Our aim was to study the relationship of GOR with autonomic function, oesophageal motility and GE in adult asthmatics.

Methods: Thirty consecutive mild, stable asthmatics (American Thoracic Society criteria) and 30 healthy volunteers underwent stationary oesophageal manometry, GE by real-time ultrasonography and autonomic function testing (cardiovascular reflex tests). GORD was assessed by symptom assessment and 24-hour pH monitoring.

Results: The asthmatics (40% male; mean age 34.8 years (SD 8.4)) and controls (50% male; mean age 30.9 years (SD 7.7)) were comparable. Twenty two (73.3%) asthmatics had increased reflux on pH monitoring. Asthmatics with higher GOR symptom scores had lesser peristaltic contractions (p=0.032), prolonged acid contact times (p<0.001), delayed GE (p=0.097) and decreased antral motility (p<0.001) than those with lower scores and controls. 69% of asthmatics showed hypergastric activity, rest had normal autonomic function, none had a hyperadrenergic response. There was no association between vagal function, oesophageal or gastric motility parameters in asthmatics.

Conclusions: A cohort of mild, stable adult asthmatics had increased GOR, decreased oesophageal motility and delayed GE. This was not associated with autonomic hypofunction, but with a hypervagal response. Our findings support the hypothesis that vagal hyperreactivity induced acid secretion leads to a reflex decrease in gastric motility, inducing GOR and secondary reduction in oesophageal motility.

P3512 Can asthma control test (ACT) replace a global assessment of asthma control according to GINA guidelines?
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Background: Asthma Control test (ACT) has been proposed as a surrogate of the assessment of asthma control, but there is controversy if it corresponds to GINA criteria (O’Byrne, ERI 2010).

Aim: To compare GINA assessment of asthma control and ACT score

Patients and methods: We evaluate 68 outpatients (33 in inhaled corticosteroids, ICO, treatment, and 35 ICO-naive), with mild-to-moderate asthma. Assessment of asthma control, but there is controversy if it corresponds to GINA criteria.

ACT score significantly correlated with SS (r=0.49), RS (r=0.46) and MA% (r=0.45), not with FEV1. ACT score only partially correlated with GINA categories of well (WC), partly (PC) and uncontrolled (UC) patients.

Contingency table between asthma control level (according to GINA Guidelines, gold standard) and ACT categories

<table>
<thead>
<tr>
<th>No.</th>
<th>ACT ≤ 19</th>
<th>ACT ≥ 19</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT score</td>
<td>25</td>
<td>24–20</td>
<td>31</td>
</tr>
<tr>
<td>Symptom Score 14 days, mean (SD)</td>
<td>5.7 (9.5)</td>
<td>3.9 (7.4)</td>
<td>13.8 (18.3)</td>
</tr>
<tr>
<td>SABA Use days, mean (SD)</td>
<td>0.5 (1.3)</td>
<td>0.5 (2.1)</td>
<td>5.1 (5.3)</td>
</tr>
<tr>
<td>No. days with MAPEF ≥10%, mean (SD)</td>
<td>1.5 (2.1)</td>
<td>2.2 (3.1)</td>
<td>3.8 (3.7)</td>
</tr>
<tr>
<td>FEV1 % pred, mean (SD)</td>
<td>96.4 (14.9)</td>
<td>92.4 (21.8)</td>
<td>98.2 (14.7)</td>
</tr>
<tr>
<td>GINA control categories WC / PC / UC</td>
<td>3/4/2</td>
<td>9/10/5</td>
<td>3/8/18/0</td>
</tr>
</tbody>
</table>

ACT ≥ 20 had high Positive Predictive Value for WC+PC (PPV: 78%), while ACT ≤ 19 had high Negative Predictive Value for UC (NPV: 89%).

Conclusion: Cut-off value of ACT has a good accuracy for detecting uncontrolled asthmatics, but not for distinguishing well from partly controlled asthmatics. The high correlations with data derived from 2-week diary card recording support ACT as a simple tool for the quantification of symptomatic asthma control.

P3513 Utility of the Hull airways reflux questionnaire in the assessment of patients in the acute admissions units
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Airway reflux and aspiration are thought to be common precipitants of acute exacerbations of COPD. A validated instrument, the Hull Airway Reflux Questionnaire (HARQ)
P3514 Investigating change in the COPD assessment test (CAT) within α-1 antitrypsin deficiency (A1ATD)

Introduction: The COPD assessment test (CAT) has been validated in COPD as a health status questionnaire (HSQ). Our group has validated the CAT in A1ATD. Further recruitment will allow us to correlate CAT scores with decline.

Methods: A1ATD patients were included in the study (n=30). CAT was completed at baseline and at six monthly time points. Associations between CAT scores and A1ATD status were investigated.

Results: There were significant associations between CAT scores and A1ATD status. The majority of patients with A1ATD had lower CAT scores compared to those without A1ATD. Significant differences were observed in the domains of activity, dyspnoea and emotion.

Conclusions: The CAT can be used as an HSQ to track change over time and whether this correlated in total CAT scores and its domains.

P3515 Associations between BODE index and systemic inflammatory biomarkers in COPD

Introduction: The BODE index is a multi-component disease and systemic inflammation represents one of the key mechanisms responsible for the systemic manifestations of this disorder, including skeletal muscle weakness and cachexia. Fat-free mass index (FFMI) which reflects better the skeletal muscle mass, has been shown to be related to both dyspnoea and exercise capacity. We hypothesized that the multi-dimensional BODE index, that reflects the multi-component nature of COPD, might be related to biomarkers of systemic inflammation. We further evaluated associations between FFMI and systemic inflammation.

Methods: BODE index and FFMI were calculated in 222 stable COPD patients and 132 smokers without COPD. Systemic inflammation was evaluated with the measurement of leptin, adiponectin, CRP, IL-6, and TNF-α in serum samples of COPD patients.

Results: In patients with COPD, both BODE index and FFMI presented significant associations with leptin levels (R2 0.66 and 0.71, respectively), whereas FFMI presented an additional association with the levels of TNF-α (R2 0.37). No significant associations were observed in normal smokers.

Conclusions: Both BODE index and FFMI are related to the circulating levels of leptin in patients with COPD, a fact that strengthens a possible role for leptin in the systemic inflammatory process of COPD. The additional association of FFMI with TNF-α further supports the closer association of FFMI with muscle wasting in COPD.

P3516 Different trends of health-related quality of life in asthma and COPD

Introduction: The progression of COPD and asthma, even though frequently overlapping, differ markedly in adult population. In general COPD is progressive, the major contributors include ongoing smoking combined with dyspnoea and disease exacerbations. In the management of COPD and asthma, monitoring of FEV1 alone does not adequately identify the high-risk patients. In this study we aimed to define the potential value of repeated measures of Health-Related Quality of Life (HRQoL) in these two diseases.

Materials and methods: Patients with asthma (N=1198) or COPD (N=601) had been recruited from two University Hospitals in Finland. Since year 2005 HRQoL had been assessed at time points 0, 1, 2 and 4 years from the recruitment by using the 15D questionnaire validated in several chronic diseases. The variation of HRQoL between the patient groups was modelled by using mixed effects models.

Results: The average trend of HRQoL separated the groups (p < 0.0003) from each other (α<0.005/year for COPD, α<0.001/year for asthma). The measures of the asthma patients developed positively or negatively regardless of their baseline 15D score, whereas those of the COPD patients tended to develop only negatively when their baseline 15D score was harmed to the level of α< 0.75 (full HRQoL α<1.0). The 15D score declined more significantly in patients who died during the follow-up period (p<0.007). The average trends in HRQoL were not different between males and females neither for the asthma (p=0.8) nor for the COPD patients.

Conclusions: HRQoL trend could serve as a valid and cost-efficient tool to identify patients who display deviant development of the disease and needs to be further investigated.
Abnormal heart rate recovery and chronotropic incompetence on submaximal exercise in COPD

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Background: A delayed heart rate recovery (HRR) after graded and an attenuated heart rate response (chronotropic incompetence, CI) are markers of cardiac autonomnic dysfunction and predict cardiovascular mortality. The latter also characterizes COPD. Therefore we hypothesized that decreased HRR and CI should coexist in COPD.

Methods: After lung function evaluation, 39 stable COPD patients and 11 healthy controls underwent submaximal cycle ergometry. Heart rate was measured at peak exercise and at 1-min recovery. Abnormal HRR was defined as a recovery of ≤12 beats in the first minute post-exercise. Chronotropic incompetence was evaluated by measuring the Chronotropic Response Index (CRI = [peak heart rate - resting heart rate]/[220 - age] - [resting heart rate]).

Results: The HRR was 13.9±3.9 beats and 23.9±5.9 beats in patients and controls (p<0.001). The CRI was 44.9±13.9 and 61.2±5.1 (p<0.01) in these groups, respectively. An abnormal HRR was observed in 29 (74.4%) of the patients.

Conclusion: A lower baseline HRR value is independently associated with a more rapid progression of emphysema and lung function decline in heavy smokers.

P3519

Abnormal heart rate recovery and chronotropic incompetence on submaximal exercise in COPD

Mans Gupta1, Vishal Bansal2, Sunil Chhabra1. 1Cardiopulmonary Physiology, Vallabhbhai Patel Chest Institute, Delhi University, New Delhi, India; 2Physiology, Vallabhbhai Patel Chest Institute, Delhi University, New Delhi, India

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P3521

Bacterial profile of acute infectious exacerbations of chronic obstructive pulmonary disease requiring hospitalization in Greece

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Bacterial infections are a major cause of exacerbations of chronic obstructive pulmonary disease (AECOPD) resulting in significant mortality and morbidity. This study was undertaken to investigate the bacterial spectrum of AECOPD requiring hospitalization.

We examined 40 patients with COPD hospitalized for infections AECOPD according to Antithenisson’s criteria. We measured lung function, and assessed sputum for infection and for bacterial using PCR. All patients had no previous intubation and none was diagnosed with pneumonia.

Examinations were hospitalized for 9 ± 4.2 days. AECOPD were associated with impaired lung function (FEV1; 42±2.0, FVC: 69±11, F EV1/FVC: 52.6±16). respiratory failure and increased sputum neu trophilia (mean ± SD; 72.7±26). PCR revealed pathogens in 88% of the sputum samples analyzed. The most commonly isolated pathogens were S. pneumoniae (65%), Haemophilus influenzae (45%); P. aeruginosa (3%). Klebsiella (7.5%) and Moraxella catarrhalis (7.5%). A mixed flora was revealed in 52.5% of sputum samples. The most common co-infection identified was by S. pneumoniae and Haemophilus influenzae (35%); followed by S. pneumoniae and P. aeruginosa (25%). In 12.5% there was a co-infection by three bacterial strains (S. pneumoniae, Haemophilus influenzae, and Ps. aeruginosa). S. pneumoniae and Haemophilus influenzae were the commonest sputum pathogens isolated in hospitalized patients with infectious AECOPD. Interestingly, in more than 50% of the cases a co-infection by 2 or three different strains was revealed.

These results should be considered when deciding the initial antibiotic treatment in Greek patients with AECOPD.
Logistic regression and linear regression were used to test for association between these SNPs and the COPD-related traits, assuming dominant (D), recessive (R) and additive (A) genetic model.

Results: Only one SNP (rs5766034) from EPHX1 showed significant association with the six-minute walking distances after Bonferroni correction (A: OR=4.08, P=0.039; OR=2.08, P=0.029). Another SNP (rs1105109) from GSTP1 showed borderline significance with anxiety symptom (D: OR=2.94, P=0.0545). The haplotype analyses validated the results from the single SNP analyses.

Conclusions: This study provides evidences that genetic variants on EPHX1 and GSTP1, two genes encoding xenobiotic metabolizing enzymes, contribute to the functional impairment of COPD in northern Chinese Hans.

P3524

Validation of a (semi-)automatic measurement- and control platform for centralized, simultaneous electronic nose (eNose) analyses in multi-centre trials

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Results: Breathing analysis by eNose technology represents a promising diagnostic tool in lung disease. The next step in making this technology suitable for multi-centre trials, such as the U-BIOPRED study, is to facilitate centralized (semi-)automatic measurements simultaneously.

Hypothesis: Incorporating multiple eNoses in a measurement- and control platform (integrated system of PC, mass flow controllers and valves) does not influence the sensor responses.

Methods: In this cross-sectional study on healthy volunteers (n = 12), exhaled breath was collected using a standardized method (Fens et al. AIRCCM 09). Two paired randomized measurements (standard configuration vs. platform) were done on two parallel eNoses (Cyrano C320). Analysis was done by linear regression (see figure).

Results: There was a slight difference in sensor responses between paired measurements. However this was proportional for all sensors. (eNose 1: 0.961 ≤ R² ≤ 0.996, eNose 2: 0.982 ≤ R² ≤ 0.998). The slopes of the linear regression lines differed when changing the sampling flow.

Conclusion: The platform has a minimal, proportional influence on sensor responses, which can be adjusted, if needed.

Implication: A parallel eNose platform can facilitate centralized, integrative analysis of different types of devices and thereby application of eNose technology on larger cohorts in a multi-centre setting.

P3525

Circadian rhythm of circulating microparticles in patients with obstructive sleep apnea

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Obstructive sleep apnea syndrome (OSAS) is considered as a risk factor to develop cardio- and cerebro-vascular diseases. Circulating cell-derived microparticles (MP) are involved in endothelial dysfunction and atherosclerosis; however, their role is not fully explored in the pathophysiology of OSAS. Eleven patients with untreated, moderate to severe OSAS (Pre-CPAP) and 7 healthy controls underwent overnight polysomnography (apnea-hypopnea index (AHI) 40±19.5 vs 24±2.2, respectively). Blood samples were collected at 11:00 AM, 5:00 PM and 9:00 PM, and then 1:30 AM and 6:00 AM on the following day. Absolute numbers of platelet-derived (CD41+) and Annexin V+ MP were measured by flow cytometry. Nine OSAS patients were re-studied after 2 months of CPAP treatment (Post-CPAP, AHI 9±1.7). Comparisons were made by repeated-measures ANOVA, and independent and paired t-test, as appropriate. Untreated OSAS patients exhibited higher levels at (5:00 PM and 9:00 PM time points) and daily variability than healthy controls both in CD41+ (p<0.05) and Annexin V+ (p<0.01) MP levels. In OSAS patients, interestingly, peak daily MP levels occurred at 5:00 PM. There was significant positive correlation between AHI and the circadian variability both of CD41+ (p<0.01, r=0.70) and Annexin V+ (p<0.05, r=0.60) MP levels. Annexin V+ and CD41+ MP counts decreased after CPAP treatment at 5:00 PM and 9:00 PM time points (p<0.01 Post-CPAP vs Pre-CPAP). Our data demonstrate that increased MP levels can only be detected at certain time points of the day in OSAS patients. The elevation of MP counts is largely reversible by CPAP treatment. The influence of circadian rhythm should be considered to assess MP levels in these patients.

3.90. Treatment beyond inhalers: endoscopic lung volume reduction

P3526

Late-breaking abstract: Prevalence of emphysema heterogeneity measured with thoracic computed tomography soft in combination with collateral ventilation assessment to plan endoscopic volume reduction

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Functional improvements after endoscopic volume reduction in severe emphysema were related to lobar heterogeneity and integrity of fissures in a post-hoc analysis of VENT data, NEJM 2010;363:1233. In 101 consecutive patients referred for endoscopic volume reduction, irrespective of CT findings, with FEV1 <50% pred. and in NYHA IV, we prospectively measured PFTs, arterial gases, % of lobar destruction as defined by the % of volume < -950 Hounsfield unit with Myriam, Intralase, Paris, France and in patients with heterogeneous disease collateral ventilation with lobar balloon Charitis, Pulmonox, USA. Patients, 75 males, were 59.1±11.4 yr old, FEV1 29.1±9.8% pred., FVC 66.8±22.1%, TLC 146.5±23.4%, PaO2 8.8±1.5, PaCO2 5.5±1.2 kPa, KCO 39.6±20.6% pred., % of destruction was 30±17 in left upper lobe, 24±18 left lower lobe, 35±21 right upper lobe, 24±20 right middle lobe and 26±20 right lower lobe. In patients with severe emphysema, lobar heterogeneity defined by at least 1 lobe with >50% destruction and a difference >10% in destruction within lobes was found in 43 cases, 22 instances in left side, 31 right side, 15 both sides with no collateral ventilation in 83%. The first patients with no collateral ventilation treated with valves experienced major improvements in 80% in terms of FEV1, FVC and weight gain. We conclude that in patients with severe emphysema, heterogeneity was found in 43% of cases. From this single centre experience, endoscopic volume reduction seemed to result in meaningful improvements in 0.43±0.80 vs 0.30±0.80 corresponding to 29% of cases. Funds from 2008-2010 innovative hospital grants.

P3527

6-month follow-up in patients with advanced upper lobe predominant heterogeneous emphysema treated with endobronchial lung sealant therapy

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Objective(s): Responses to AeriSeal® Emphysematous Lung Sealant System (ELSS) therapy in patients with advanced upper lobe predominant heterogeneous (ULP) emphysema are summarized out to 6 months of follow-up.

Methods: 14 patients with ULP emphysema received ELSS treatment in a multicenter study conducted at 8 sites across Europe and Israel. Ten (10) of these...
P3528

Physiological consequence of lower vs upper lobe lung volume reduction in patients with advanced emphysema

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Objectives: Lower lobe lung volume reduction in patients with advanced emphysema has been associated with greater clinical benefit that upper lobe therapy. We present computer modeling results that explain these observations, and can help direct treatment site selection in patients undergoing lung volume reduction therapy.

Methods: Our model considers alveoli as discrete units with an exponential pressure-volume relationship of the form (V(Ptp) = Vmax – A e-kPtp). Gravitational effects on transpulmonary pressure (Ptp), the extent of tissue destruction, airflow closure effects, and extent of heterogeneity were incorporated as independent variables to predict RV and RV/TLC.

Results: Gravitational effects on Ptp are the major determinant of residual RV and overall RV/TLC. In upper lobe heterogeneous emphysema, changes in Ptp from volume reduction distend the remaining alveoli at end exhalation. However, RV and RV/TLC are reduced due to a decrease in the total number of diseased alveoli following treatment. In lower lobe heterogeneous emphysema, volume reduction distends already stretched upper lobe alveoli attenuating treatment effects on gas trapping. This phenomenon was more pronounced in homogeneous disease. Potentially beneficial effects of lower lobe volume reduction could be completely negated by upper lobe alveolar distension, resulting in no improvement, or even worsening of RV and RV/TLC despite alveolar resection.

Conclusions: Gravitational effects largely explain why lower lobe volume reduction therapy is less therapeutic than upper lobe therapy. In patients with homogeneous emphysema, lower lobe therapy can actual worsen gas trapping despite resection of diseased tissue.

P3529

Effect of fissure integrity on the efficacy of bronchoscopic lung volume reduction therapy using a peripheral-acting tissue sealant in patients with advanced heterogeneous (ULP) emphysema

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Objective(s): The study examines how fissure integrity affects the response to endobronchial volume reduction therapy (ELV), a peripheral-acting tissue sealant.

Methods: The model considers alveoli as discrete units with an exponential pressure-volume relationship of the form (V(Ptp) = Vmax – A e-kPtp). Gravitational effects on transpulmonary pressure (Ptp), the extent of tissue destruction, airflow closure effects, and extent of heterogeneity were incorporated as independent variables to predict RV and RV/TLC

Results: ELS therapy in patients with advanced ULP emphysema improves lung function, functional capacity and quality of life out to at least 6 months. Improvements in spirometry were observed in 9 of 14 patients at 6 month follow-up. Physiological responses were best in those patients (n=10) who received bilateral upper lobe split dose therapy. Changes in FEV1 were (ΔFEV1 = +24.8±36.8%; ΔFEV1/FVC = +17.6±25.6%).

Conclusions: ELS therapy in patients with advanced ULP emphysema improves to those observed following bilateral upper lobe volume reduction surgery.

P3530

Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness

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Background: Bronchoscopic thermal vapor ablation (BTVA) ablates emphysema tissue through a localized inflammatory response followed by contractive fibrosis and atelectasis leading to permanent lung volume reduction that should not be influenced by collateral ventilation.

Objectives: To determine the correlation of clinical data from a trial of BTVA to patients with advanced ULP emphysema. Method: Single arm study (n= 44) of patients with heterogeneous upper lobe predominant emphysema with FEV1 <45% predicted. Patients received BTVA to the RUL or LUL in a single setting. Primary efficacy outcomes: FEV1, and SGRO at 6 months. Efficacy: lobar volume reduction (LoVR) from thin section multislice CT, spirometry, body plethysmography, 6MW and mMRC dyspnea score. The treated lobar fissure was analyzed visually in non-enhanced pre-interventional CT. Results: Incomplete fissures of small fissure, upper half of right large fissure, and three fissures of left large fissure were estimated in 5% increments and the relative amount of fissure incompleteness was calculated. Pearson correlation coefficients were calculated for the association between fissure incompleteness and change in efficacy outcomes (baseline to 6 months).

Results: Mean age 62 years, 50% men, FEV1 0.85 L (31% predicted), SGRO 59 up (66% predicted). Calculated relative fissure incompleteness was 13% (median; range 0-63%); 38/44 patients (86%) had fissure incompleteness. Correlation coefficients (r) for the association of incompleteness to outcomes are as follows: FEV1: 0.17, LoVR -0.27, SGRO -0.10, 6MW 0.0, RV -0.18, RV/TLC -0.14

Conclusion: BTVA induced LoVR and improvements in clinical outcomes are independent of fissure integrity.

P3531

Associations of efficacy outcomes following bronchoscopic thermal vapor ablation (BTVA) for the treatment of heterogeneous emphysema

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Objective(s): The associations among various COPD efficacy endpoints are variable; however, the degree of correlation is often important in examining the consistency of the results across measures that are not considered redundant.

Methods: Single-arm trial of BTVA in patients with upper lobe predominant emphysema. Patient criteria: FEV1 15% -45% predicted, age 40-75 yrs, RV >150%, TLC<100%, 6 minute walk distance (6MWD)>140 m, DLCO<20%, previous pulmonary rehabilitation. Primary efficacy endpoints: FEV1, and St. George’s Respiratory Questionnaire total score (SGRO) at 6 months. Other endpoints: body plethysmography, mMRC dyspnea, 6MW. Pearson correlation coefficients were calculated for the association of changes from baseline to 6 months of physiological measures and LoVR to health outcomes.

Conclusions: Fissure integrity had minimal impact on the overall response to endobronchial lung volume reduction therapy performed using ELS in patients with advanced ULP emphysema.

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Results: 44 patients received BTV. Mean age: 63 years, men 50%, FEV1 0.86 (31% predicted), RV 237% predicted, DLCO 35% predicted, SGRQ 59 units, 6MWD 300 m. n=24 R, n=20 L.

Conclusion: Physiologic and CT LoVR outcomes correlate strongest with the BODE score and the perception of dyspnea. The variable degree of correlation among the health outcomes indicates the need to examine multiple efficacy variables in emphysema and reinforce that the measures are not redundant.

P3532

Efficiency of the endo-bronchial volum reduction treatment for heterogeneous lower lobe predominant emphysema

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Background: Patients with severe chronic obstructive pulmonary disease (COPD) have limited treatment options. Exercise capacity and health related quality of life (HRQL) of these patients are affected by the progress of respiratory failure. Thus, there is a need for new treatments that can palliate. Endo-bronchial volum reduction treatment (EBVRT) which is a minimally invasive method has been come up. Endobronchial valves (EBV) that allow air to escape from a pulmonary lobe but not enter. It can induce a reduction in lobar volume that may thereby improve lung function and exercise tolerance in patients with advanced emphysema.

Methods: To evaluate the safety and effectiveness of the EBVRT of lower lobe predominant heterogeneous emphysema. Functional capacity was evaluated with spirometry, 6minute walk distance (6MWD). SGRQ were applied to evaluate the HRQL.

Result: Five patients with heterogeneous lower lobe predominant emphysema (two left, three right lower lobes) were treated with EBV. Most of the patients were males (80%). The mean age was 65 years. Valves were placed into left lower lobe (n=2) and right lower lobes (n=3). Valves were placed in airways with 100% technical success. There were no procedure-related deaths and complications. At the third month after therapy there was an increase in 4.6% in the forced expiratory volume 1 second (FEV1) and 2.3% increase of 6MWD were observed. Also, there was a decrease of 2.3% in the SGRQ score was observed.

Conclusion: EBVRT for heterogeneous lower lobe predominant emphysema patients induced modest improvements in lung function, exercise tolerance, and HRQL. EBVRT is a new safety method for the patients with severe COPD.

P3533

Multi-stage endobronchial valve treatment of emphysema

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Of 59 patients with emphysema treated with endobronchial valves (EBV) at our institution, nine were submitted to multi-stage strategies with placement of additional valves at varying intervals to complement initial treatment or compensate for inadequate early results. Twenty patients (P3531) were treated with EBV alone.

Results:

Patient No. BODE* 1st treatment Interval 2nd treatment Initial Final Results:

A

Baseline to 1 month after insertion

B

1 month to 6 months

C

6 months to 2 years

D

2 years to 5 years

E

5 years to 10 years

F

10 years to 15 years

G

15 years to 20 years

H

20 years to 25 years

I

25 years to 30 years

J

30 years to 35 years

K

35 years to 40 years

L

40 years to 45 years

M

45 years to 50 years

N

50 years to 55 years

O

55 years to 60 years

P

60 years to 65 years

Q

65 years to 70 years

R

70 years to 75 years

S

75 years to 80 years

T

80 years to 85 years

U

85 years to 90 years

V

90 years to 95 years

W

95 years to 100 years

X

100 years to 105 years

Y

105 years to 110 years

Z

110 years to 115 years

**Values were completely removed for one month

Multi-stage strategies should be considered in all valve patients as part of their treatment approach.

P3534

Management of severe COPD patients using bronchoscopic valve lung volume reduction: Preliminary results

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Background: Despite of a modern level of anesthesiology, reanimation and surgical techniques lethality after LVRS remains on range 2.5% and level of complications in some clinics reaches 20%.

Aim: To fulfill a technique of bronchoscopic valve lung volume reduction (BLVR) in management of COPD patients, to develop indications and contra-indications.

Materials and methods: 9 patients are undergone BLVR. Mean age was 56 y. All have severe dyspnee from 3 up to 4 points on scale MRC, FEV1 - 25-63%, TLC - 134±25%, RV - 287±34%, a distance in 6-min test - 245±54 m. Criteria of inclusion in BLVR program were similar to those at a LVRS. Procedures were performed under local anesthesia with intravenous potentiation. Intervention carried out on one lung in 1 case, 2 patients undergone consecutive bilateral BLVR.

Results: Endobronchial volum reduction treatment (EBV) for heterogeneous bronchial tube of the most emphysematic segment or bronchial tubes of adjacent lobes for prevention of air bypass. The quantity of valves on one procedure varied from 1 up to 2. Average duration of procedure was 35±12 minutes.

Results: All patients were discharged. Average hospital period was 4 days. 2 patients had severe atelectasis in situ of valve. 2 patients had severe COPD exacerbation. 6 patients had marked reduction of dyspnee, improving quality of life, increasing of physical tolerance, keeping up to 12 months after BLVR, including FEV1 - 30±5%, TLC - 102±3%, RV - 247±14%.

Conclusion: Preliminary results of BLVR indicates safety and expediency of BLVR in management of carefully selected severe COPD patients. We consider BLVR as a treatment option before LVRS and IT.

P3535

Endoscopic lung volume reduction (ELVR) with the “endo-bronchial Miyazawa valve” (EMV) in patients with severe emphysema, a prospective pilot study

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Introduction: The ELVR represent a new minimally invasive palliative option for the treatment of severe emphysema. The EMV is a new device with different characteristics compared to the others (a simple all in silicone structure, with a large opening, inexpensive, and without special delivery system) and is little studied.

We believe this unidirectional valve is effective in reducing lung hyperinflation and improving lung function and dyspnea of a subtype of emphysema patients. We report here the data at one month for the first two patients.

Method: Patients are affected from severe (FEV1<40%) heterogeneous emphysema and major hyperinflation (>130%). The Outcomes are the adverse effects, lung functions, exercise capacity and quality of life. The EMVs have been inserted through a rigid bronchoscopic in the target segmental or lobar bronchi supplying the most hyperinflated part of the lung in order to achieve an unilateral treatment with lobar exclusion.

Results: Baseline to 1 month after insertion. The patients A and B have improved in quality of life (Casey’s respiratory questionnaire A 9.8±18 points, pulmonary function FEV1 0.51 to 0.62L and F0 0.9 to 1.4L, RV A 4.49 to 2.53L and B 5.6 to 5.2L. DLCO A 38 to 55.2% B 25 to 33% of predicted value) and exercise capacity (6 min. walk test A 65±m B 120±m). No atelectasis was visible on radiological control but signs of air trapping were reduced.

Adverse effects: Two episodes of bronchosopasm in the first patient well controlled by medical therapy, and none in the second.

Conclusion: Our preliminary encouraging experience describe a new tool for the therapy of selected emphysema patients.

P3536

Comparison between Chartist® pulmonary assessment system detection of collateral ventilation vs. corhal CT fissure analysis in predicting atelectasis in emphysema patients treated with endobronchial valves

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Introduction: Accurancy of the Chartist® Pulmonary Assessment System in identifying responders after endobronchial valve (EBV) treatment is the subject of a recently concluded multi-center European study. The Chartist system quantifies collateral ventilation (CV) by sealing a lung compartment and measuring its air pressure and flow. When the resistance value <0.1 the patient is “CV Positive”, when the resistance value ≤0.10, the patient is “CV Negative”. Fissure analysis
prediction of LVR response is based on “completeness” or “incompleteness” of the target lobe fissure. In this study, the predictive value of the HRCT vs. Chartis assessment is compared.

Objective: To determine whether the accuracy of CV assessment is comparable to fissure analysis from HRCT in predicting clinically significant LVR following EBV treatment.

Methods: Baseline and 30-day follow-up HRCTs of EBV treated patients were evaluated by an independent, blinded core lab(s). A Chartis assessment was conducted prior to the baseline core lab reading. The baseline HRCT fissure results and the Chartis assessments were compared for a “reliability” prediction, and reviewed against the LVR in the treated lobe as measured by 30-day HRCT.

Results: Data for 31 patients is available to date. Analysis of up to 75 patients is expected for ERS. In 31 patients, Chartis and CT matched 24 times (77.4%). Chartis and CT did not match 7 times (22.6%).

Conclusion: Accuracy of the Chartis® System is comparable to Corelab review of HRCT, and may be used in lieu of fissure analysis to predict clinically meaningful LVR following EBV treatment.

P3537
Bronchoscopic assessment of collateral ventilation predicts outcome of endoscopic lung volume reduction with valves
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Background: Collateral Ventilation (CV) is a cause of failure of endoscopic lung volume reduction (ELVR) with endobronchial valves. The Chartis system (PulmonX, USA) measures CV in the target lobe of ELVR to predict outcome and aid patient selection.

Aims: To test this hypothesis we correlated Chartis values with outcome of ELVR with EBV.

Methods: In 15 patients with severe heterogeneous emphysema we measured CV with Chartis in the target lobe of ELVR and achieved complete lobar exclusion with Zephyr®. We measured lung function, 6MWD, SGRQ and radiological outcome at baseline and one month.

Results: In 2 patients a valid Chartis signal was not obtained. 3 patients showed high CV (Chartis value < 10 vs. CV < 10) and 10 patients low CV (Chartis value > 10 vs. CV < 10). The CVve group compared to the CVve group showed significant improvement of obstruction (ΔFEV1 0.23±0.13 L vs. -0.05±0.18 L; p=0.018) and hyperinflation (ΔRV -0.12±0.72 L vs. 0.02±2.78 L; p=0.037). Δ6MWD was 58.6±43.3 m (ns) and ΔSGRQ was -10.5±2.0 (ns). 10/15 patients had a response to EBV (8 CVve vs. 2 without valid Chartis signal). Atelectasis developed in 8/15 patients (CVve, 2 without valid Chartis signal). Of the 5/15 non-responders the Chartis value was <0 vs. >10. CVve group had a response to EBV (8 CVve vs. 2 without valid Chartis signal). Of the 5/15 non-responders the Chartis value was <0 vs. >10.

Conclusions: In our patient cohort Chartis adequately predicted outcome of ELVR with EBV in 11/15 patients. In 2 patients a valid Chartis measurement could not be obtained. 2 patients, although the Chartis reading was interpreted as CV-ve, were non-responders. Despite these limitations, Chartis in our preliminary experience seems a valuable tool to select patients for ELVR with EBV.

P3538
One year follow-up of intra-bronchial lung volume reduction in alpha-1-antitrypsin deficiency and severe emphysema
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Introduction: In patients with alpha-1-antitrypsin (AAT) deficiency, severe emphysema mainly localized to the lower lobes can develop. Volume reduction surgery (LVR) is not recommended in these patients.

Objectives: One-way valves in selected bronchi can reduce the size of hyper-inflated lung areas, and we decided to make a pilot study of intra-bronchial volume reduction (IBVR) in patients with AAT deficiency and severe lower lobe disease.

Methods: In patients aged 40-80 years, with RV >150% and FEV1<15% of predicted, and predominantly lower lobe disease, IBRV with installation of 3-4 valves in one selected lower lobe was performed.

Results: Five patients were included. There were no complications. An immediate improvement, both subjectively and objectively, occurred and remained during the six months the patients have been followed. FEV1/sec increased from a mean of 0.76 to 1.2 L (57%) and RV decreased from 5.5 L to 4 L (42%).

Conclusion: IBRV seems to be a safe, reversible, and simple method to improve lung function in selected patients with AAT deficiency. Further studies are warranted.

P3539
Endobronchial identification of persistent peripheral bronchopleural fistula with digital chest tube monitoring followed by treatment with endobronchial one-way valve implantation
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Introduction: Bronchopleural fistula (BPF) is associated with high morbidity and mortality and causes prolonged hospital stay and costs. Surgery remains the treatment of choice, however, many patients are at high risk or unwilling to undergo thoracotomy.

Objectives: To present a standardized approach of endobronchial and treatment of persistent peripheral BPF.

Methods: 10 patients with persistent air leaks (presence of chest tube >7 days) underwent bronchoscopy with balloon occlusion technique and digital monitoring of airflow in order to identify the peripheral source of bronchopleural fistula. Endobronchial one-way valve implantation (Spiration Inc., Olympus) was performed in a segmental or subsegmental level to block ventilation to the BPF.

Results: Mean chest tube drainage time prior to the intervention was 22±13 days. The source of the BPF was endoscopically identified in all cases. Bronchoscopic valve implantation (1.6±0.8 valves per patient) was performed successfully in all patients. Using digital chest tube monitoring air flow immediately decreased from ≥0.026±0.095ml/min to ≤56.7±1ml/min (p < 0.001), indicating successful cessation of the leakage. 2 patients underwent additional chemical pleurodesis. The chest tube was removed 8.5 days after bronchoscopy. There was no evidence of recurrence during a mean follow-up time of 2 months.

Conclusion: Using a standardized approach in endobronchial diagnosis followed by endobronchial one-way valve implantation results in a high responder rate in patients with peripheral BPF.

P3540
Bronchoscopic injection of absolute ethanol in patients with persistent air leak from chest tube drainage
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Background: Chest tube drainage (CTD) has indicated for the treatment of pneumothorax, hemothorax and after thoracic surgery. But, in the case of incomplete lung expansion and/or persistent air leak from CTD, medical or surgical thoracoscopy or, if that is unavailable, limited thoracotomy should be considered.

Objectives: To test this hypothesis we correlated Chartis values with outcome of ELVR volume reduction (ELVR) with endobronchial valves (EBV). The Chartis system (PulmonX, USA) measures CV in the target lobe of ELVR to predict outcome and aid patient selection.

Methods: In 15 patients who had persistent or prolonged air leak from CTD were included. In 11/15 patients. In 2 patients a valid Chartis measurement could not be obtained. 2 patients, although the Chartis reading was interpreted as CV-ve, were non-responders. Despite these limitations, Chartis in our preliminary experience seems a valuable tool to select patients for ELVR with EBV.

Results: 15 patients (all men) were enrolled. There were 14 spontaneous pneumothorax (5 idiopathic, chronic obstructive pulmonary disease (COPD) and 3 post-tuberculosis) and 1 empyema associated with broncho-pleural fistula in the study. Of 14 patients with ethanolamine injection therapies, five had previous medical therapy, wedge resection for bullae, but the others didn’t have. Twelve were successfully treated by an ethanolamine injection therapy alone. But three (idiopathic, COPD and post-tuberculosis) were failed and followed by a surgery (2 cases) or pleurodesis (1 case). Minor complications such as fever, chest pain and transient pneumonic infiltrations occurred after the therapy. With successful, the time to dischare was about 3 days (median).

Conclusions: Bronchoscopic ethanol injection therapy may be partially useful in controlling air leakage and reducing the hospital stay in patients with CTD.

P3541
Results of BODE index in the European multicenter study for the treatment of advanced emphysema with bronchial valves
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The BODE index evaluates the risk of mortality in patients with COPD. The VENT study (un-blinded, randomized with a medical control arm) reported that at 6 months. 40.6% of subjects treated with the Zephyr® (Pulmonx) valve in a single lobe, achieved at least a 1-point improvement in the BODE index as compared with only 18.6% of controls. We reported positive results of a blinded and randomized sham bronchoscopy controlled study evaluating the IBV® valve system (Spiration) treating both upper lobes in subjects with advanced emphysema but, without the goal of lobar atelectasis.

Methods: BODE was calculated at baseline and 3-months (blinded study period) in subjects in whom all necessary data was available.

Results: With the exception of 1 subject in the treatment group (TG), blinding was maintained. BODE improvement was -0.32±1.4 and -0.33±1.1 in the TG and CG respectively (p>NS). Approximately half of the TG had improvements that may reflect treatment and positive study effects. In contrast with the not-blinded VENT control arm, 36% of the CG had improvements that could only be explained by positive study effects and/or placebo.
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391. Molecular markers: diagnosis and management of malignant pleural effusions

P3543
Expression of ERK2 and p38α kinases in pleural mesothelial cells after exposure to asbestos fibers.

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Asbestos is known to stimulate gene expression in a variety of cell types via down-stream intracellular signaling cascades. This mechanism includes the mitogen-activated protein kinases, which can lead to increased transcriptional activation of genes related to cell proliferation, apoptosis and inflammation.

Objectives: To quantitively and to compare the expression of ERK2 and p38α in pleural mesothelial cells (PMC) exposed to crocidolite or chrysotile fibers.

Materials and methods: C57/B6 mice received intrapleural injection of crocidolite or chrysotile fibers (3.0 μg/cm²) or PBS (control). After 1, 7, 14 and 30 days the animals were euthanized and PMC were extracted. ERK2 and p38α levels were measured by ELISA. Results are expressed in mm ± SD using t-test (p < 0.05).

Results: In the control group ERK2 and p38α levels were undetectable. Both crocidolite and chrysotile stimulated PMCs to produce, as shown in the table.

Conclusions: Our data demonstrated that crocidolite produced higher levels of ERK2 and p38α than chrysotile, in a time-dependent fashion. More studies are needed to examine whether activation of this pathway is functionally linked to cell inflammation and cellular apoptosis induced by asbestos fibers and its role in the carcinogenesis of mesothelioma.

P3544
Prognostive value of promoter hypermethylation of tumor suppressor genes in malignant pleural fluid

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Background: To determine the prognostic value of promoter hypermethylation of p16/INK4a, MGMT, BCR/ABL and RAR β genes in pleural fluid (PF) and other clinicopathological parameters in malignant pleural effusion (MPE).

Methods: We evaluated 49 patients. We recorded clinical characteristics, characteristics of the PF, the detection of promoter hypermethylation of the tumor suppressor genes in PF by methylation-specific polymerase chain reaction.

Results: We included 37 (75.5%) lung cancer patients and 12 (24.6%) with other epithelial neoplasia. The median time of global survival was 255.5 (IC 95%:56-488.5) days. Parameters associated with a minor survival were: the presence of others metastasis (p=0.003); no chemotherapy treatment (p=0.001); pH<7.28 (p=0.004); glucose<60 (p=0.002) and the absence of some methylated gene (p=0.003). After the univariate analysis, chemotherapy treated have a significantly reduced risk of death (OR=0.05; p = 0.001). Patients with metastasis (OR 5.1;p=0.001) and patients with pH<7.28 (OR=3.2;p=0.003) have more risk of death. Chemotherapy treatment received (OR=0.1;p=0.001) and the presence of methylated genes (OR=0.2;p=0.002) were factors associated with major survival in patients with lung adenocarcinoma diagnosed.

Conclusions: In patients with lung adenocarcinoma, the presence of promoter hypermethylation of genes and history of chemotherapy treatment were significantly associated with major survival. Tumor extension, not having received chemotherapy and the characteristics of the PF were factors related to the risk of death in all MPE patients analyzed.

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P3545
Endogenous thrombin potential (ETP) in pleural effusions

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The coagulation system plays an important role in the physiopathological mechanisms of inflammatory diseases compromising the pleural space. Endogenous thrombin potential (ETP) is a new marker used to evaluate coagulation system that recording hypercoagulability, as well as, hypo-coagulability and reflects quantitatively the measure of generated thrombin.

Objective: To evaluate the ETP in pleural effusions of different etiologies.

Methods: Thirty seven patients with pleural effusion were enrolled, previous to any treatment: 10 Lung cancer (LC), 6 breast cancer (BC), 11 tuberculosis (TB) and 10 transudates (TD). ETP in plasma (P) and pleural fluid (PF) were quantified by using the BCS system (Siemens, Germany). The results (mAU) were calculated by mathematical derivation from the kinetic reaction developed where

533s
ETP is expressed by the area under the curve (AUC). Statistical analysis: One Way Anova.

Results: In plasma, the ETP levels were lower in the TD group. In pleural fluid, the higher levels were observed in the BC group. However, considering the pleural effusions altogether, no statistical differences were observed between transudates and exudates.

ETP levels in plasma and pleural fluid

<table>
<thead>
<tr>
<th>LC</th>
<th>BC</th>
<th>TB</th>
<th>TD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>407 ±18.8</td>
<td>425 ±54.1</td>
<td>350 ±38.5</td>
<td>285 ±72.2</td>
</tr>
<tr>
<td>PF</td>
<td>75 ±62.72</td>
<td>249 ±78.39</td>
<td>123 ±55.56</td>
<td>77 ±19.49</td>
</tr>
</tbody>
</table>

*p<0.05

Conclusion: This preliminary result shows that ETP may be useful to characterize the fibrinolytic response of the pleural space in inflammatory conditions. A greater number of malignant and infectious exudates need to be studied to better understand the real usefulness of ETP in the mechanism of pleural effusion formation, as well as, the management of therapeutic approach.

Support: CNPq, FAPESP

P3S46 Diagnostic and prognostic significance of survivin levels in malignant pleural effusion

Didem Görgün1, Funda Şeviş1, Kenan Midilli2, Vakur Akkaya1, Pinar Yıldız1, Carmen Manta1, Paola Ferro2, Enrico Battolla3, Maria Cristiana Franceschini2, Leslie Kulikowski2, Vanessa Alvarenga1, Roberta Sales1, Francisco Vargas2, Massimiliano Sivori1, Silvia Simonini4, Alessandra Bonotti5, Franco Fedeli2, Lisete Teixeira1, Leila Antonangelo1,2, Julia Puka1, Roberta Sales1, Francisco Vargas1, Evaldo Marchi2, Leslie Kulikowski2, Vanessa Alvarenga1, Roberta Sales1, Francisco Vargas2, Lisete Teixeira1, Leila Antonangelo1,2, Julia Puka1, Roberta Sales1, Francisco Vargas1, Evaldo Marchi2, Leslie Kulikowski2, Vanessa Alvarenga1, Roberta Sales1, Francisco Vargas2, Lisete Teixeira1, Leila Antonangelo1,2, Julia Puka1, Roberta Sales1, Francisco Vargas1

Objective: To evaluate the expression of ProGRP in pleural fluid (PF) of patients with malignant pleural effusion (MPE).

Methods: ProGRP was quantified by chemiluminescence immunoassay with microcrystals (CMIA, Architect, Abbott) in PF (collected in EDTA tubes) from 49 patients with MPE (45) and benign effusions (4). Malignant samples corresponded to pleural metastasis of: neuroendocrine lung carcinoma (3), breast (7), lung adenocarcinoma (20), lung poorly differentiated carcinoma (4), bronchioloalveolar adenocarcinoma (1), and others (10). Benign cases corresponded to paraneoplastic (3) and lupus-related effusions (1).

Results: Considering 4 levels, we obtained: 0 to 46 pg/mL: 37 (75%); 47 to 100 pg/mL: 4 (8.2%); 101 to 200 pg/mL: 2 (4.1%) and > 200 pg/mL: 6 (12.2%) of the cases. The benign cases and most of the metastatic effusions were in level 1. All cases in level 2 corresponded to lung adenocarcinoma. In level 3, one case corresponded to a poorly differentiated lung carcinoma and one to bronchioloalveolar adenocarcinoma. In level 4, two cases were poorly differentiated lung adenocarcinoma, and one was a sarcoma of the osteosarcoma. The remaining 3 cases corresponded to tumors of neuroneuroendocrine lineage. In these cases, the concentration of ProGRP was higher than 30,000 pg/mL.

Conclusion: PF ProGRP can be useful in identifying pleural metastasis of undifferentiated tumors. Although a greater number of cases should be studied, it seems unequivocal its importance in recognizing neuroendocrine lineage tumors.

P3S47 The value of mesothelin in pleural effusion vs histology by medical thoracoscopy

Carmen Manta1, Paola Ferro2, Enrico Battolla1, Maria Cristina Franceschini2, Massimiliano Sivori1, Silvia Simonini4, Alessandra Bonotti5, Franco Fedeli2, Silvio Roncella1, Per Aldo Casanella1,1 Pneumology, San Bartolomeo Hospital, Sarzana, La Spezia, Italy; 2Histopathology and Cytopathology, San Bartolomeo Hospital, Sarzana, La Spezia, Italy; 3Clinical Pathology, San Andrea Hospital, La Spezia, Italy; 4Preventive Medicine, a5 Spazio, La Spezia, Italy; 5Preventive Medicine, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Results: Survivin level was 40.32±7.56 in MPE, 15.83±10.92 in TPE and 8.33±6.7 in TE. According to survivin level there was no statistical significant difference been study groups. (p=0.182). When the patients divided two group as malignant and non-malignant pleural effusion, survivin level was significantly higher in MPE (40.32±7.56) than in non-MPE (13.33±2.05) (p=0.011). The cut-off value for survivin levels detected by ROC curve analysis was 7.5 pg/mL, with sensitivity 87.5%, specificity 86.7%.

Conclusions: There was no correlation between survivin level and age, sex, location, fluid pH, glucose, protein, albumin and ADA level while there was significant correlation with fluid LDH. (r=0.045; p<0.001). No correlation between survivin levels and survival were detected in MPE.

In conclusion, survivin expression levels detected with ELISA can be useful for the differential diagnosis of MPE and non-MPE despite TPE can cause false positive results in high prevalent countries. Specificity and sensitivity results could be better when cases of tuberculosis has been ruled out. Further studies are needed which included larger group of patients with other exudative effusions.

P3S48 Epidermal growth factor (EGF) and VEGF levels in pleural effusion

Massimiliano Sivori1, Silvia Simonini4, Alessandra Bonotti5, Franco Fedeli2, Liliana Libanori1,2, Chiara Corda3, Maria Cristina Franceschini2, Carlo Pirozzi1, Liliana Libanori1,2, Chiara Corda3, Maria Cristina Franceschini2, Carlo Pirozzi1

Results: Eighty-two patients with pleural effusion were included: 30 tuberculosis (Tb), 25 malignant (Ca) and 25 transudates (Trans). Pleural fluid levels of MPMs (1, 2, 8 and 9, TIMPs (1 and 2), VEGF, IL-6 and TGF-β1 were quantified by ELISA. Statistical analysis: One Way Anova and Spearman’s correlation.

Results: Except MPM-1 and TIMP-2, all parameters were higher in exsudates than transudates. MPM-8, MPM-9 and IL-6 levels were higher in Tb than Ca or Trans. The better correlation between MPMs and cytokines were observed in Tb group (MMMP-9 x TGF-β1 and MMP-9 x VEGF).

MMPs, MPMs and cytokines in pleural effusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tb</th>
<th>Ca</th>
<th>Trans</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPM-1</td>
<td>488 ±180</td>
<td>531 ±178</td>
<td>84 ±16</td>
<td>0.314</td>
</tr>
<tr>
<td>MPM-2</td>
<td>271 ±524</td>
<td>156 ±10</td>
<td>166 ±10</td>
<td>0.009</td>
</tr>
<tr>
<td>MPM-8</td>
<td>2037 ±388*</td>
<td>1026 ±289*</td>
<td>109 ±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEGF</td>
<td>11290 ±204*</td>
<td>603 ±144*</td>
<td>79 ±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6</td>
<td>1903 ±64*</td>
<td>1856 ±40*</td>
<td>720 ±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>227 ±8</td>
<td>232 ±9</td>
<td>229 ±8</td>
<td>0.918</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>686 ±76*</td>
<td>321 ±52*</td>
<td>840 ±105</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: Most of the MPMs and TIMP-1 seems to be involved in the pathogenesis of tuberculous and malignant pleural effusion. The correlation between MPM-9 and TGF-β1 could be related to the pleural thickness observed in some cases of tuberculosis.
P3550
Diagnostic yield of cytology in malignant pleural effusion: Impact of volume and repeated thoracocentesis
Mehrdad Soltoki. Internal Medicine-Pulmonary Division, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Pleural effusions are a common finding in patients with cancer, and the diagnosis is important in view of prognosis and management. We conducted this study to determine the sensitivity of pleural fluid cytology and also to check the minimum volume required for best diagnostic yield of cytology and the effect of repeated thoracocentesis on the results.

Methods: This prospective - descriptive study in patients with exudative pleural effusion during a period of 24 months (from September 2007 to August 2009) had been admitted in massih-daneshvari hospital in Tehran-The patients underwent thoracocentesis and pleural fluid cytology and subsequently followed up for six months. Diagnostic value of cytology in general and also of different volume of pleural fluid and impact of repeated thoracocentesis were investigated.

Results: A total of 318 patients were studied. Sensitivity of cytology for diagnosis of pleural malignancy was 40.8% (p=0.004). The sensitivity of first, second and third cytologic exam was 11.6%, 16.8% and 23.8% respectively. Sensitivity of tests with increasing the volume of fluid was increased (p=0.004).

![Image](59x158 to 289x158)

![Image](59x274 to 289x275)

![Image](59x286 to 289x287)

![Image](59x598 to 289x598)

P3551
Clinical and laboratory variables useful in the differential diagnosis of pleural effusions secondary to tuberculosis or lymphoma
Robert Sailes1, Francisco Vargas1, Lisete Teixeira1, Roberto Ouniishi1, Eduardo Lapa1, Leila Antongiulio Oliveira1,2,3 Pulmonary Division - Pleura Laboratory, Heart Institute (InCor) - University of Sao Paulo Medical School, Sao Paulo, Brazil,1LIM 01 - Clinical Laboratory Pathology Department, University of Sao Paulo Medical School, Sao Paulo, Brazil

Tuberculosis (TB) and Lymphoma (LYM) represent two important causes of lymphocytic effusions. Due to the similarity of clinical and laboratorial features between these clinical conditions, the differential diagnosis frequently represents a challenge to the physicians.

Objective: To describe clinical and laboratory variables capable in differentiating these diseases.

Methods: We analyzed pleural fluid of 159 patients with TB or LYM. Clinical (gender, age and symptoms), Biochemical (glucose, protein, LDH, cholesterol, triglycerides, amylase and ADA) and Cytological analyses were evaluated.

Results: In both groups there was a male predominance. Age and symptoms duration were significantly higher in LYM patients, while complaining of night sweats was more common in TB.

![Image](307x559 to 537x560)

![Image](307x586 to 537x587)

![Image](307x598 to 537x598)

P3552
Approach to undiagnosed exudative pleural effusion: The diagnostic yield of blind pleural biopsy
Mehrdad Soltoki, Majid Malekmohamad. Internal Medicine, Shahid-Beheshti University of Medical Science, Tehran, Islamic Republic of Iran

Blind pleural biopsy has traditionally been performed to investigate the etiology of exudative pleural effusion in which the initial thoracocentesis has been non-diagnostic. This study examines the role of blind Abrams pleural biopsy in investigation of the exudative pleural effusion in the largest tertiary pulmonary center in Iran (Massih-Daneshviri Medical Center).

Method: All patients with pleural effusion admitted from September 2007 to April 2009 entered a prospective cohort study. Patients with exudative pleural effusion underwent blind Abrams pleural biopsy if the initial thoracocentesis was non-diagnostic. Patients with non-diagnostic blind biopsy underwent surgical biopsy or other investigations based on physicians decision.

Results: Blind percutaneous pleural biopsy were performed in 171 patients. For all diagnoses, blind biopsy had a sensitivity of 70.1% and negative predictive value of 14.8%. For malignancy and TB diagnosis, sensitivity value was 58.9% and 88.1% and negative predictive value 63.2% and 93.6% respectively. Overall malignancy was diagnosed in 95 (58.6%) and TB in 59 (36.4%) of patients.

Sensitivity, specificity, and positive and negative predictive values of blind pleural biopsy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity* (%)</th>
<th>NPV** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>58.9 (48.9, 68.3)</td>
<td>63.2 (53.7, 71.8)</td>
</tr>
<tr>
<td>TB</td>
<td>88.1 (75.9, 94.1)</td>
<td>93.6 (87.4, 96.9)</td>
</tr>
</tbody>
</table>

*M=0.004 based on Chi-square test (P=0.001 for trend test). **M=0.012 based on Chi-square test (P=0.001 for trend test).

Conclusions: Blind Abrams needle biopsy was diagnostic in approximately three out four patients presenting with undiagnosed exudative pleural effusion. The data support the use of the Abrams needle in the investigation of pleural effusion especially in less developed countries.

P3553
Diagnostic comparison between pleural fluid cytology (PFC), cellular block (CB) and pleural biopsy (PB) under visual guidance
Cristina Fernandez1, Karen Czischke2,4, Gerardo Morejovic3, Gabriél Cavada4, Maite Oyayan3, Roberto Gonzalez3, Andrea Retamal1.
1Pathology, Instituto Nacional del Tórax, Santiago, Chile; 2Respiratory Medicine, Instituto Nacional del Tórax, Santiago, Chile; 3Thoracic Surgery, Instituto Nacional del Tórax, Santiago, Chile; 4Internal Medicine, Universidad de Los Andes, Santiago, Chile

PFC is the less invasive method for diagnosing pleural neoplasms and the reported sensitivity is 50%.

Methods: All patients evaluated at our institution who had PFC and CB done between May 2009 to June 2010 and had PB indicated where included in the study. Diagnostic categories were specified for the analysis of PC and CB. The pathologist who read the PFC and CB was blind to the PB final diagnosis. The accuracy of the techniques was compared to PB.

Statistical analysis: Kappa (k) index was used to evaluate the concordance between the different techniques versus the PB and the concordance between PFC and CB. The sensitivity and specificity for malignancy was established for every technique.

Results: 92 patients were included in the study. The PB was positive in 71 (77%) cases. The PFC was positive in 42 (45.6%) and the CB was positive in 35 (38%) of the cases. PB/PFC agreement was 68.5%; k=0.49. PB/CB agreement was 61.5%; k=0.32. PFC/CB agreement was 84.6%; k=0.68. Eleven out of 12 effusions with PFC suspicious of malignancy turned out to be malignant when compared to PB and all the suspcious CB where malignant in the PB. For PFC sensitivity was 64.3%, specificity was 100%, with a positive predicted value (PPV) of 100% and a negative predicted value of (NPV) 45%. For CB sensitivity was 59.2%, specificity was 100% with a PPV of 100% and a NPV of 42%.

Conclusion: There is good agreement between PFC and CB for the diagnosis of malignancy. CB trends to agree more than PFC with PB in the diagnosis of pleural mesothelioma. The sensitivity and specificity of PFC in the diagnosis of malignancy is similar to what is reported in the literature.

P3554
The role of video-assisted thoracoscopy in the diagnosis of malignant pleural mesothelioma
Ivan Novakov1, Silviya Novakova2, Iryko Peshev3, Maija Pirgowa3.
1Thoraco-Abdominal Surgery, Medical University, Plovdiv, Bulgaria; 2Intr-Costal Consultant Department, Medical University, Plovdiv, Bulgaria; 3Clinical Pathology, Medical University, Plovdiv, Bulgaria

The diagnosis of malignant pleural mesothelioma still remains difficult, because it needs to be differentiated from pleural metastasis and pleural benign diseases. The aim of the study is to demonstrate and find out the opportunities of video-assisted thoracoscopy to obtain the diagnosis of malignant pleural mesothelioma.

Materials and methods: 23 patients with malignant pleural mesothelioma, complicated with pleural effusion were included in this 5-year study. Video-assisted thoracoscopy was performed in all patients. Pleural effusion, obtained through thora-
coscopy, was sent for cytological analysis. Parietal pleural biopsies were performed through thoracoscopically. Histological examination of hematoylin-eosin stained pleural tissue sections was performed. Three markers with positive diagnostic value (anti-cytokeratin 5/6, vimentin, S-100) were used for immunohistochemical examination.

Results: Video-assisted thoracoscopic showed multiple nodules on parietal pleura in all patients. Histologically, in 15 cases malignant mesothelioma was classified as epithelial, and in other 8 as biphasic type. Final diagnosis malignant pleural mesothelioma was confirmed by immunohistochemistry in all cases.

Conclusion: We demonstrate that video-assisted thoracoscopic allows complete visual examination of the pleura in cases of malignant mesothelioma without pleural symphysis. Multiple and large pleural tissue specimens can be obtained through video-assisted thoracoscopic, which provides the diagnosis of malignant mesothelioma.

P3555
Diagnostic thoracoscopic in suspected malignant disease of the pleura: Pleural nodularity justifies talc poudrage
Wulf Harmes, Bernd Schönhofer. Pulmonary Medicine, KRH Klinikum Oststadt-Heidehaus, Hannover, Germany

Introduction: In a patient with suspected malignant pleural effusion and negative pleural fluid cytology, medical thoracoscopic is the next diagnostic step. Confirming the diagnosis of malignant disease involving the pleura usually means incurable cancer. Talc poudrage during the diagnostic thoracoscopic would be a reasonable approach to gain efficient pleurodesis and to reduce patient discomfort due to repeat thoracoscopies that would be necessary in the case of recurrent pleural effusion. However, in most institutions instantaneous section histology is not available. Thus, a visual diagnosis of malignant pleural disease would be desirable. The aim of our study was to find out if it is possible to differentiate between benign and malignant pleural disease simply by evaluating pleural nodularity.

Results: Between 11/2006 and 10/2007 we performed 81 medical thoracoscopies. 41 patients had a benign disease of the pleura and 40 had a malignant disease of the pleura. Pleural nodularity was noted in one benign case (a singular node) and in 29 malignant cases (four with a singular node, eleven with some nodes, and 14 with many nodes). Sensitivity for malignancy with the visibility of nodules was 72.5% and specificity was 97.6%. The positive predictive value for malignancy with one visible node was 80% and with some or many nodes 100%.

Conclusions: Nodularity is a strong predictor of pleural malignancy. If some or many nodes are visible during medical thoracoscopy, immediate talc pleurodesis is justified. However, in about one quarter of the cases of pleural malignancy, no nodularity was noted and for these cases immediate talc poudrage cannot be recommended.

P3556
Review of respiratory physician inpatient pleural ultrasound service
Burhan Khan, Majid Mushtaq. Department of Respiratory Medicine, Dartford Valley Hospital, Dartford, Kent, United Kingdom

Introduction: The appropriate and timely investigation, interventions and management of pleural effusions remains discrepant with variable practices and pathways, possibly impacting upon quality of care. Aims: To ascertain the qualitative and quantitative outcomes of running a Respiratory physician led inpatient pleural ultrasound service.

Methods: A prospective analysis of 12-18 month experience in a district general hospital of providing an inpatient pleural service by chest physicians with thoracic ultrasound.

Results: From May 2010 to date (10 months) 111 patients were included. We compare the pleural disease activity level pre and post establishing of this service.

Table 1. Overview Pre & Post establishing Inpatient Pleural Ultrasound Service

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>May 2010 to Feb 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of Radiology Department Pleural Ultrasound</td>
<td>93</td>
<td>113</td>
<td>6</td>
</tr>
<tr>
<td>Number of “X” marks the spot by Radiology</td>
<td>13</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Number of Physician ward based Pleural Ultrasound</td>
<td>0</td>
<td>82</td>
<td>29</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>79</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

The remit and breadth of inpatient pleural service and interventions undertaken are as follows.

Table 2. Type of Inpatient Pleural Ultrasound & Intervention

<table>
<thead>
<tr>
<th>Type / Intervention</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic US (No intervention)</td>
<td>35</td>
</tr>
<tr>
<td>Pre Medical Thoracotomy</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostic pleural aspiration</td>
<td>33</td>
</tr>
<tr>
<td>Therapeutic pleural aspiration</td>
<td>22</td>
</tr>
<tr>
<td>Diagnostic &amp; Therapeutic pleural aspiration</td>
<td></td>
</tr>
<tr>
<td>US guided intercostal chest drain</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
</tr>
</tbody>
</table>

Conclusion: Provision of an inpatient pleural service does require work planning and resources but results in qualitative and quantitative improvements in patient care including: improved clinical practices by avoiding “X” marks the spot; pleural interventions done quicker and safely with no complications to date; and improved pathways for patients with pleural disease.

P3557
Safety and efficacy of pleurodesis with thoroscopic doxycycline poudrage in malignant pleural effusion
Mohamed Elhady, Amr Sakr. Chest, Cairo University Hospitals, Cairo, Egypt

Objective: To assess the safety and efficacy of thoroscopic doxycycline poudrage (TDP) for pleurodesis in malignant effusions.

Design: Retrospective.

Methods: Twenty seven patients were included in this study. Thoracoscopy was performed for diagnosis and subsequent doxycycline pleurodesis. At the end of thoracoscopy, a new method for Doxycycline delivery to the pleura was used through pneumatic atomizer insufflations where about 500-1000 mg of doxycycline were taken & prepared as a powder from the oral preparation (vibramycin 100 mg/capsule).

Results: 74.1% had a successful pleurodesis, 18.5% had partial response and 7.4% had failed pleurodesis at one month. Adverse effects included pain (48.1%), fever (3.7%) and pain & fever (22.2%). The mean drainage time for intercostals tube was about 1.52 days.

Conclusions: TDP is an inexpensive, well tolerated, reasonably effective, comparatively simple, safe, and capable of alleviating respiratory symptoms.

P3558
Audit of chest drains for pleural effusions in a tertiary care centre
R. Naseer, P.K. Plant, M.E.J. Callister. Respiratory Medicine, St. James University Hospital, Leeds, West Yorkshire, United Kingdom

Background: Pleural effusion is a common clinical problem with malignant effusions likely to become an increasing burden. Recent guidelines recommend chest drains (ICDs) for effusions are performed under US guidance, written consent is obtained & only in emergencies should ICDs be placed out of working hours. Over the last 24 months we have introduced a structured ultrasound training programme for respiratory trainees & a chest drain course for juniors.

Method: We audited ICDs for effusions in June & July 2010 in a tertiary centre. Results: There were 32 ICD’S inserted in 28 patients (pts) with a mean age of 71.62.5 Female, 37.5 Male. 56% Right & 44% Left sided. 32% had known malignant effusion. Of the 68% with an undiagnosed effusion 53% had known malignancy & 33% had an end diagnosis of malignancy. 36% were placed out of working hours. Only 2 patients were pleurectomised.

Summary of results

<table>
<thead>
<tr>
<th></th>
<th>All Drains (n=13)</th>
<th>Respiratory Oncology/hematology (n=11)</th>
<th>Other (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion team</td>
<td>72% radial</td>
<td>38% radial</td>
<td>100% radial</td>
</tr>
<tr>
<td></td>
<td>22% resp</td>
<td>62% resp</td>
<td>60% radial</td>
</tr>
<tr>
<td></td>
<td>6% other</td>
<td>9% other</td>
<td>40% other</td>
</tr>
<tr>
<td>USS guidance</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>92%</td>
<td>92%</td>
<td>60%</td>
</tr>
<tr>
<td>Written consent</td>
<td>38%</td>
<td>92%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>92%</td>
<td>60%</td>
</tr>
<tr>
<td>CXR post procedure</td>
<td>99%</td>
<td>92%</td>
<td>29%</td>
</tr>
<tr>
<td>Dedicated ICD observation chart</td>
<td>34%</td>
<td>85%</td>
<td>0%</td>
</tr>
<tr>
<td>Complication rate</td>
<td>22%</td>
<td>13%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>(all drain fail out)</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>chest tube radiology</td>
<td>72%</td>
<td>38%</td>
<td>100%</td>
</tr>
<tr>
<td>resp: respiratory</td>
<td>60%</td>
<td>60%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Conclusion: Respiratory education helped achieve adherence to guidelines for patients managed by respiratory medicine, however a large number of ICD’S are inserted by radiology and a significant number are being managed by Oncology. Therefore effective management of pleural effusions requires close liaison with & education of other specialties with local pleural guidelines formulated through consultation with radiology and oncology.

P3559
Efficacy of talc pleurodesis in patients with malignant pleural effusions
Ismaila Alraddad, Nathan Reyes, Javier Gallego, Juan Cotera, Isabel Caballero, Desire Macias. Respiratory Unit, Valme University Hospital, Seville, Spain

The aim of this study was to analyze complications and survival after talc pleurodesis for recurrent malignant pleural effusion. Methods: All patients with proven malignant pleural effusion who received talc pleurodesis from January 2004 to August 2010 were included in a retrospective analysis. Talc pleurodesis was performed with talc slurry if the pleural effusion was known previously as neoplastic or under medical thoracoscopic with talc pleurodesis from January 2004 to August 2010 were included in a retrospective study. Results: Twenty seven patients were included in this study. Thoracoscopy was performed for diagnosis and subsequent doxycycline pleurodesis. At the end of thoracoscopy, a new method for Doxycycline delivery to the pleura was used through pneumatic atomizer insufflations where about 500-1000 mg of doxycycline were taken & prepared as a powder from the oral preparation (vibramycin 100 mg/capsule).

Results: 74.1% had a successful pleurodesis, 18.5% had partial response and 7.4% had failed pleurodesis at one month. Adverse effects included pain (48.1%), fever (3.7%) and pain & fever (22.2%). The mean drainage time for intercostals tube was about 1.52 days.

Conclusions: TDP is an inexpensive, well tolerated, reasonably effective, comparatively simple, safe, and capable of alleviating respiratory symptoms.
Postoperative pleural drainage was used until fluid output was less than 100 ml/24 h. 

Results: 54 patients (30 male and 24 female) with mean age 65.9±12.5 (range 36-91) years were included. The most common primary cancer sites were lung (13 cases), mesothelioma (9), gynecological (7), digestive (8), and unknown primary (9). Six patients (11%) developed thrombosis (four in the cava vein). Two patients developed empiema and other two bronchopleural fistula. In 7 cases pleurodesis was ineffective and in nine cases pleural effusion relapsed. In 17 cases was complete success (32%) and in 21 partial success (39%). Patients with Karnofsky index (KI) < 60% had greater survival [10.71 months 95%CI (7.34-14.08)] than patients with KI less than 60% [2.52 months 95%CI (0.20-4.84)]

Methods: We used data from the population-based Austrian Burden of Obstructive Lung Disease (BOLD) study. Participants were aged >40 years and completed post-bronchodilator spirometry. Risk factors for COPD and respiratory symptoms were recorded. A clinical history indicating COPD was defined as the presence of one or more risk factors and any concomitant respiratory symptom(s). 

Results: Among 1258 participants 255 (20.3%) reported presence of one or more risk factors and presence of one or more respiratory symptoms, and were therefore considered to present with a clinical history indicating COPD. Among those the proportion of airways obstruction defined by FEV1/FVC<LLN and FEV1/FVCO<0.70 was 26% and 39%, respectively. Altogether 99 (7.9%) subjects presented with a clinical history indicating COPD and FEV1/FVC<0.70, while 65 (5.2%) presented with a clinical history indicating COPD and FEV1/FVCO<LLN.

Discussion: Utilization of the LLN as a threshold for the FEV1/FVC ratio would identify approximately two thirds of subjects with a clinical history indicating COPD and GOLD-defined disease. The response not identified when using the LLN would have mild disease (GOLD stage 1).

393. COPD diagnosis

P3561
Should we use FEV1/FVC < 0.70 or FEV1/FVC < LLN to identify subjects with a clinical history indicating COPD? – Results from the population-based BOLD study in Salzburg, Austria

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Rationale: To compare the fixed ratio of 0.70 and the LLN to identify subjects presenting with a clinical history indicating COPD. 

P3562
A Dutch web-survey on management of malignant pleural effusions

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Background: Malignant pleural effusion (MPE) is a major problem in patients with advanced cancer. Pleural approximation is necessary for a successful pleurodesis. The decision to perform a pleurodesis is made by the pulmonologist. Inter-physician variances in the assessment of the Chest X-ray might have impact on the final outcome of the pleurodesis procedure.

Aims and objectives: To describe decision variability among physicians regarding pleurodesis.

Methods: A series of 50 consecutive chest X-rays made during MPE drainage with clinical data were sent to all active Dutch pulmonologists, together with a questionnaire on the MPE management. The following questions were asked for all of these X-rays: (1) Do you report this lung to be expanded? (2) Would you install a sclerotic agent? (3) What would be the estimated chance on a successful pleurodesis?

Results: Pulmonologists of 30% of the Dutch hospitals responded. All pulmonologists were aware of the national guideline. The overall probability of recommending a pleurodesis was higher in the expanded lung group than in the not expanded lungs (90 vs 39%; p<0.0001). More experienced pulmonologists (more vs. less than 100 drains per year) less often reported a fully expanded lung (49 vs 57%; p=0.03), but were likely to recommend pleurodesis more often (probability was 95 vs 85% patients with a fully expanded lung and 44 vs 32% for an incomplete expanded lung; p=0.06). All pulmonologists assessed the success rate for breast cancer higher than for other tumors (p=0.002), and they tended to recommend pleurodesis more often in this group (p=0.07).

Conclusion: Pulmonologists’ experience influences decisions regarding MPE management.

P3563
Clinical COPD questionnaire (CCQ) score and mortality

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Introduction: Quality of life is an important patient-oriented measure in COPD. The Clinical COPD Questionnaire (CCQ) is a validated instrument for estimating health status, correlating well with instruments such as SGRQ and SF-36. The prognostic qualities of CCQ have not been evaluated. This study investigated the association of CCQ with all-cause mortality in COPD patients.

Methods: A total of 1548 patients with a diagnosis of COPD were randomly selected from 70 Swedish primary and secondary care centres. The analysis included 956 patients (aged 34-75 years). Information was collected using questionnaires and record review. The Swedish Board of Health and Welfare provided mortality data. Cox regression estimated survival with adjustment for age, sex, smoking, education, level of care, and lung function (only available for a subset with spirometry data, n=491).

Table 1. Mortality according to phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Median age at inclusion</th>
<th>Mortality rates</th>
<th>Mortality: Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype 2</td>
<td>68</td>
<td>708 (89%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Phenotype 3</td>
<td>59</td>
<td>17/87 (20%)</td>
<td>2.73 (1.13; 6.60)</td>
</tr>
<tr>
<td>Phenotype 4</td>
<td>72</td>
<td>21/85 (25%)</td>
<td>3.34 (1.14; 7.87)</td>
</tr>
<tr>
<td>Phenotype 5</td>
<td>58</td>
<td>15/83 (35%)</td>
<td>4.50 (1.83; 11.3)</td>
</tr>
</tbody>
</table>

Risk ratios with phenotype 2 as reference.

Conclusion: These data provide strong evidence that our previously identified phenotypes have different natural history.
Methods: 730 current- or ex-smokers including 382 COPD subjects were studied (66.7±11.0 yrs, 602male/128 females). We collected the data for all the subjects on pulmonary function test, 6 minute walking test (6MWT), body mass index (BMI), dyspnea (modified Medical Research Council (MMRC) Dyspnea Scale, Oxygen Cost Diagram (OCD)), and the extent of emphysema and airway disease assessed by chest computed tomography (CT) (low attenuation area (LAA)% and wall area (WA)%), and we also studied the data on the score of St. George’s Respiratory Questionnaire (SGRQ) for QOL (n = 361), and exacerbations (n = 178). We performed a principal component analysis (PCA) and cluster analysis by k-means method.

Results: PCA showed the major factors as follows: vital capacity (VC), LAA%, WA%, reversibility, PaO2, PaCO2, leg fatigue on 6MWT. Cluster analysis with these factors classified the subjects into four clusters as follows: Cluster 1; 254 cases with mild emphysema (LAA% < 22.1%, WA% < 10.8, BMI < 18.5), Cluster 2; 156 cases with airway disease (LAA% 15.7±11.3, WA% 58.3±12.8), Cluster 3; 152 cases with emphysema and airway disease (LAA% 20.1±13.2, WA% 6.5±11.5), Cluster 4; 168 cases with severe emphysema (LAA% 41.0±11.8, WA% 57.0±11.3).

Cluster 4 has the highest SGRQ score (p < 0.0001). Cluster 2 and 4 were more prone to exacerbations (p < 0.05).

Conclusions: PCA and cluster analysis revealed that chest CT contributes to the classification to subpopulations in smoker with or without COPD.

P3567 Spirometry in UPLIFT®: Quality and reproducibility over time

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Background: UPLIFT® was a 4-yr, randomized, double-blind, placebo-controlled multicenter trial in 5993 patients (pts) with chronic obstructive pulmonary disease (COPD).

Aims and objectives: To explore spirometry quality and reproducibility in this large trial.

Methods: Within-test variability of pre- and post-bronchodilator (BD) forced expiratory volume in 1s (FEV1) was within-patient measurement error of acceptable maneuver in 1 spirometry, compared across study visits. Between-test variability was mean difference of best pre- or post-BD FEV1 values across 2 visits (6 mo interval), corrected for normal decline 1.5±1L. At trial start (a), middle (b) and end (c).

Results: 3 acceptable maneuvers in 93.8% visits. Within-test variability of pre- and post-BD FEV1 (mean SD: 0.092L and 0.098L) decreased during the trial (visits 3-19; figure), a similar pattern seen in analysis of pts with measurements at all visits. Between-test variability decreased over time: pre-BDFEV1 (a=0.14±0.13L; b=0.13±0.12L; c=0.12±0.12L) post-BD-FEV1 (a=0.14±0.14L; b=0.13±0.12L; c=0.12±0.12L), and was dependent on age, sex, smoking status, GOLD stage, but NOT BD response or treatment (isotropium/control).

Conclusion: Spirometry quality in UPLIFT® was excellent and improved during the trial. Large interoccasion variability dependent on age, sex, smoking and COPD severity suggests relevant cut-offs for individual disease monitoring are hard to establish.

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P3568 Discriminative characteristics of the CAT score in stable COPD patients

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The CAT score is a new tool to assess health-related quality of life in patients with COPD. Its discriminative characteristics are yet to be described.
Clinical-morphological changes in bronchial mucous membrane according to the III-IV COPD stages

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Aim: To estimate the depthness, intensity and reversibility of structural changes in bronchial walls in III-IV COPD stage with immunomorphological method using.

Study design: 42 pts (mean age 59 ± 1.7 years) with COPD: 1 gr - 30 pts with III stage (20 male), II gr - 12 pts with IV stage (9 male). Bronchoscopy with consequent histology sampling and assessing by microscopy and immunohistochemistry (ICC) research was done for all pts. The following indexes were evaluated: Ki-67 (reflect proliferative potential and activity of epithelial regeneration); Cytokeratin 8 (Ck) (as a marker of glandular epithelium); Ck 34E12 (squamous epithelium origin).

Results: In Gr I all pts had been demonstrated intensive positive membrane reactions with Ck 8 in uninnuriosuous ciliary and basal epithelial cells and heterogeneous positive membrane reactions with Ck 34E12. The simultaneous co-expression of both types of cytokeratins indicates the reversibility of metaplasia.Histological investigation: hypertrophy of smooth muscles, polypoid overgrowthing of mucous, proliferation of fibroblasts.

In Gr II took place focal positive membrane reaction with Ck 8 in residual glandular cells, and intensive expression of Ck 34E12 without co-expression of both markers.

Conclusion: 1. Pts with COPD III had been estimated changes with high reversibility, but with provided exclusion trigger agents and relevant therapy, in comparison with COPD, stage IV. 2. Pts with COPD, stage IV, the atrophy and sclerosis of bronchial walls were revealed. Immunomorphological data indicated about regenerating depletion and permanent irreversible changes of bronchial tree.

Impairment of membranous and vascular components of pulmonary diffusion and plasma endothelin-1 in patients with liver cirrhosis with and without COPD

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Liver cirrhosis (LC) may be rarely complicated by hepatic pulmonary syndrome or hypertension. Nevertheless abnormalities of gas exchange are frequent in LC. The mechanisms are still unclear. A reduced hepatic clearance of Endothelin – 1 is playing a role.

In 72 pts with LC, 29 (40.3%) of whom had accompanying COPD, PFT were performed as well as measurements of PaO2, diffusion capacity, pulmonary capillary blood volume (Qc), membrane diffusing capacity (Dm) and plasma ET-1. The functional measurements were performed in a matched group of pts with COPD without liver function impairment (n=38).

None of the pts. had clinically manifest hepatic pulmonary syndrome or hypertension. Liver cirrhosis B 7.02% (81.9%) of the pts. with LC and all pts. with both LC and COPD and 31/39 (79.5%) pts. with sole COPD showed decreased TLC.

In all pts. but one with sole LC Dm was reduced. Qc was reduced to a lesser extend in 47 (65.2%) pts., with a greater impairment of Dm. In the COPD group the reduction of Dm was the overwhelming mechanism of an abnormal diffusion capacity PaO2D was significantly negatively correlated with TLC, Qc and to a lesser extend with Dm in pts. with LC without ventilatory impairment. All pts. with LC independently on coexisting COPD showed increased plasma concentrations of ET-1, which were negatively correlated with Qc (r=0.5, p=0.015).

Impact of the DM as a responsible for an abnormal gas exchange in pts. with LC contrary to COPD where reduction of Dm plays the most important role. Increased ET-1 in LC might contribute to pathogenesis of gas exchange impairment in LC.

Clinical characteristics of COPD with mild bronchiectasis

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Aim: We tested the hypothesis that patients who have COPD and develop mild BE have a more deteriorated QOL, exercise capacity, and outcome after 1 year than those patients who have COPD without bronchiectasis (BE).

Methods and subjects: The study population consisted of 204 consecutive patients with COPD. All the patients underwent HRCT of the chest and the following studies: quantitative assessment of bronchiectasis by using the methods reported by Bliha (1991) and Smith (2010), pulmonary function tests, 6-minute walking test, and assessment for QOL. The outcomes for acute exacerbations were evaluated for 1 year.

Results: The study included 204 patients (men, 189; women, 15) with a mean age of 71.2 years. The prevalence of BE in the patients was 27% (n = 55), and the frequency of exacerbations (FE) was 0.49 per year for 70 of the patients. On adjusting for FEV1%, age, and gender, it was found that the patients who had COPD and BE had significantly higher FE than those who had COPD without BE (p = 0.01). Visual analogue scale-QOL assessments indicated a trend towards deteriorated QOL for patients with BE with regard to social activity alone. The fat free mass index for patients with BE was significantly lower than that for patients without BE (p = 0.02). These data were almost similar for the 2 different assessments performed using the methods reported by Bliha and Smith.

Conclusions: The patients who had COPD with mild BE had greater likelihood of acute exacerbation than did the patients who had COPD without BE. This characterized phenotype of COPD that is attributed to BE should be evaluated for chronic management even in mild cases of BE.
Results: Our study group consisted of 55% males, mean age of 63.9±8.2 years, mean FEV1 of 46.8±17.2%, pred, median BODE of 4 (2-5) and median CCI of 1.0 (0-7.5). Mean AF was 3.4±0.7AU and correlated positively with age (p<0.01). We found no difference in AF between sex, GOLD criteria, BODE index and CCI. No correlation with FEV1 was observed, but AF was positively correlated with the amount of pack years smoked (r=0.278, p<0.05). In multivariate regression analysis age and pack year smoked predicted AF for 16%.

Table 1. Linear regression of severe COPD patients (n=100) with skin autofluorescence as dependent variable.

<table>
<thead>
<tr>
<th>Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²=0.16</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
</tr>
<tr>
<td>Amount of pack years</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Conclusion: Although AF correlated with age and the amount of pack years smoked in a group of severe and complex COPD patients, AF was not associated with any criteria of disease status, suggesting that AF is not a good marker of disease status.

P3574
Association between comorbidities, disease severity and body mass index in COPD patients
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Background: COPD patients are often afflicted by multiple comorbidities. Objectives: To assess the nature and prevalence of comorbid diseases in a COPD population and to study the association between comorbidities and COPD severity and disease duration.

Methods: We studied 470 patients who met GOLD spirometric criteria for COPD (post-bronchodilator FEV1/FVC < 0.7). Data on comorbidities and pulmonary function tests were collected. Subjects were stratified by GOLD stage (GOLD I–IV) and body mass index (BMI) as underweight (BMI<21; n=119), normal-weight (n=115), overweight (BMI>25–30; n=130) and obese patients (BMI>30; n=95). Data are presented as mean (SD): Spearman test Kruskal-Wallis test were used.

Results: Of the patients studied, 281 were men (59.8%), with mean age of 64.9 (10.3) years, FEV1 of 1.31 (0.3) l and BMI of 25.3 (5.7) kg/m². The average number of comorbidities per patient was 3.1 (1.9). In 105 patients (22.3%) five or more comorbidities were identified. The most frequent comorbidities found were hypertension (44.9%), cardiac disease (20%), diabetes (14.7%), osteoporosis (13.6%) and dyslipidemia (13%). There was no correlation between COPD severity and number of comorbidities (p>0.05). There was a significant correlation between BMI and number of comorbidities (r = 0.323; p < 0.001). Obese patients had an average of 4.1 comorbidities, and overweight, normal-weight and overweight patients of 2.8, 2.5 and 3.1, respectively.

Conclusion: We found that comorbidities are frequent in COPD and are associated with increase of BMI. Therefore, COPD patients should be encouraged to maintain their weight in the normal range. Supported by FIFE/HCPA and FAPEGO.

P3575
Features of mucous membrane changes of bronchial tree at patients with COPD
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Aim: Research was an estimation of expressed of changes of mucous membrane of bronchial tree at patients of COPD on the different stages of pathologic process. Study population: We investigated 86 patients (pts) (53 male, mean age 62.4±4.4 yrs) with COPD. All pts were divided on three groups: 1 group (gr.) – 10 pts with COPD I stage (st); II gr. – 28 pts with II st.; III gr. – 36 pts. with COPD II–IV stage (st). The state of mucous membrane of bronchial tree, degrees of atrophy of epithelium, character and amount of mucus, was estimated.

Results: We found that comorbidities are frequent in COPD and are associated with increase of BMI. Therefore, COPD patients should be encouraged to maintain their weight in the normal range. Supported by FIFE/HCPA and FAPEGO.

P3577
Comorbidities associated with chronic obstructive pulmonary disease (COPD) – A clinical study
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OPD continues to be one of the commonest causes of increasing morbidity and mortality globally. While cardiovascular (CVD) and cerebrovascular diseases are decreasing over the years, COPD is the fourth leading cause of death, thanks to continuing smoking habits, atmospheric and industrial pollution. Lack of awareness and late diagnosis adds to injury. Associated comorbidities such as CVD, muscle/cerebral disorders and infective exacerbations are not often recognised.

P3578
Evaluation of the gas exchange abnormalities in COPD patients with the use of capnometry
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Background: COPD is airway disorder associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Due to progressive nature of the disease the respiratory failure verification is of great importance.”
Objectives: This study aimed to investigate capnometry indices in patients with stable COPD (GOLD III-IV) compared to healthy subjects.

Methods: capnometry, capnometry. Data are presented as mean±SD.

Results: A total of 87 subjects (age 56.2±1.2 years; 59% male) were enrolled: COPD group (n=42, mean±%FEV1 =39.5%), control group (n=45, mean±%FEV1 =93.7%). All subjects were performed bodyplethysmography and capnometry, we compared the results between groups. All bodyplethysmography and capnometry indices of COPD subjects were significantly (p<0.05) different from control. The mean values Rtot,%= 241.6±12.7 and 117.7±4.8, R2 = 81.1±2.2 and 110.9±3.2, R5V = 189.9±9 and 101.1±5 in COPD and control group respectively. The capnometry results were Vd/VE=VT 33.8±1.2 and 25.5±1.1, PEFCO2, kPa = 2.8±0.1 and 3.2±0.1, end-expiratory lung volume, was 5.1±0.2 and 4.7±0.2, FE2CO2% = 0.3%±0.1 and 3.4±0.1 in COPD and control group respectively.

Conclusions: Capnometry might be a useful tool to detect the respiratory failure in COPD patients.

P3579

The indices of body composition (IBC) in chronic obstructive pulmonary disease (COPD)

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The aims: To analyze of IBC at different stages of COPD as well as the relationships between the IBC, lung function and smoking status.

Material and methods: Bone mineral content (BMC), Fat mass (FM) and Lean mass (FM, excluding BMC) were detected by dual-energy X-ray absorptiometry. FM, FFM and BMC were expressed as the ratio to height squared to obtain indices FM/H2, FFM/H2 and BMC/H2 respectively. (The pts of 1st group 49, 50 and 53 respectively; of 2nd group 14, and 15; of 3rd group 20 and 21). The control group was formed of 15 healthy men (mean age 56 yrs, mean BMI 26 kg/m2, smokers 84%, pack/yrs 28). The control group was subdivided into 3 groups according to COPD severity. The 1st group was made of 14 men (GOLD I stage; mean age 55 yrs; FEV1 78%, BMI 27 kg/m2, smokers 68%, packyears 69), the 2nd group included 43 men (GOLD II stage; mean age 57, FEV1 63%, BMI 28 kg/m2, smokers 80%, pack/yrs 21); the 3rd - 20 men (GOLD III stage; mean age 60; FEV1, 41%; BMI 24 kg/m2, smokers 84%, pack/yrs 28). The control group was formed of 15 healthy men (mean age 56 yrs, mean BMI 26 kg/m2, smokers 66%, pack/yrs 20).

Results: The BMI value was decreased during COPD progression (from 21,3 kg/m2 in the 1st group to 17,7 kg/m2 in the 3rd group: p<0.05). We revealed the significant correlations between: COPD severity and FFMI (r = -0.54); FMI, FFMI, BMCI and packyears (r = -0.37, -0.38, -0.3 respectively). FFMI level was higher in 1st and 2nd groups as compared to the control and FFMI significantly correlated with FVC (r=0.4) and FEV1 (r=0.4). The BMCI value in 1st group and the control was similar (1.06 kg/m2) and it was significantly higher than in 2nd and 3rd groups (1.01 and 0.89 kg/m2 respectively). Pts of 3rd group had a lower FMI as compare with the pts of 1st and 2nd groups (4.25 vs. 8.28 and 9.72 respectively; p<0.05).

Conclusions: The IBC changes can probably reflect COPD progression.

P3580

Evaluation of different domains of the Saint George’s respiratory questionnaire (SGRQ) according to the severity levels of chronic obstructive pulmonary disease (COPD)

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Relevance: Spirometric parameters used to determine disease severity may not be appropriate to infer about the different components of functioning in patients with COPD.

Purpose: To compare and correlate the scores of the different SGRQ domains according to the GOLD severity levels in patients with COPD.

Methods: A cross-sectional study was conducted at a hospital university. Comparison (Kruskal-Wallis) and correlation (Spearman) tests were used after performing normality tests. This study was approved by the Ethics Committee.

Results: Table 1 summarizes the data for each GOLD stage. No significant difference was observed between stages I and II or I and III for any of the SGRQ domains. There were no significant correlations between FEV1 and the SGRQ scores. Conclusion: The results suggest that there is no linearity between the severity levels of COPD and the SGRQ scores, including the activity and psychosocial impact domains.

P3581

Fibroblast growth factor 23 (FGF23) and hypophosphatemia in patients with COPD

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Introduction: Previous studies highlighted the importance of phosphate depletion in COPD patients and the association between correction of hypophosphatemia and improvement in respiratory muscle function. Fibroblast Growth Factor 23 (FGF23) is a recently discovered circulating protein that plays a crucial role in renal phosphate reabsorption and body phosphate regulation. FGF23 has been investigated in several diseases but there is currently no published data about FGF23 in COPD.

Aims and objectives: The aim of this study was to evaluate whether FGF23 levels correlate with serum phosphate levels and disease severity in COPD patients.

Methods: 70 COPD patients aged 63±4.6 years and 34 age and sex matched randomly selected controls were studied. Criteria for diagnosing COPD and assessing severity were according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines. Serum samples were analyzed for routine tests including calcium, phosphate, renal/lytes, and FGF23 levels were measured by a commercially available Eliza kit.

Results: There were no differences in serum calcium and Vitamin D levels in COPD patients and controls (P = 0.05). COPD patients had significantly lower serum phosphate levels compared to controls (P < 0.01). Plasma FGF23 was significantly higher in patients compared to controls: 280 (51-968) versus 140 (21-200) RU/ml (P < 0.001). As expected plasma FGF23 levels correlated negatively with serum phosphate (r = 0.799 & P < 0.001). Furthermore plasma FGF23 correlated negatively with FEV1 (r = 0.352 & P = 0.003).

Conclusion: This study illustrates a significant increase in plasma FGF23 levels that may contribute to low phosphate levels and disease severity in COPD patients.

P3582

Low testosterone in chronic obstructive pulmonary disease

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Aim: Among other comorbidities, COPD patients have fatigue and a low physical activity level. A low level of testosterone may explain some complaints mentioned by COPD patients. In this study we compared the testosterone level in COPD patients with that of elderly men with a normal pulmonary function.

Methods: Circulating levels of testosterone and luteinizing hormone were determined using chemiluminescence technique in 34 patients (FEV1: 34.9% of the predicted values) and 20 control subjects. Moreover, the relationship of hypogonadism with 6-min walking distance, number of pack-year, systemic inflammation and LDL level has been studied in men with COPD.

Results: The testosterone level was lower in the COPD patients (p =0.001; <0.05). Low androgen status was related to LDM, level and 6-min predicting walking distance. No correlation was observed between testosterone level and FEV1, CRP level, and number of pack-year.

Conclusion: Testosterone level is significantly lower in COPD patients comparing with control subjects. A restricted activity level is in correlation with testosterone level. Further studies are necessary to clarify the hypothesis that testosterone treatment could enhance the COPD patients activity level.

P3583

WITHDRAWN
P3584
The study of proton magnetic resonance spectroscopy on hippocampus in rats with chronic obstructive pulmonary disease
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Objective: To employ in vivo proton nuclear magnetic resonance spectroscopy to investigate the hippocampal metabolism of rats with Chronic Obstructive Pulmonary Disease and to assess if there is a relationship between brain metabolism and chronic brain injury in COPD.

Methods: Rats COPD model (model group, n=6) were established by passive smoking and intratracheal instillation of lipopolysaccharide (LPS). Other groups were compared with controls (n = 6), and all subjects underwent brain micro-magnetic resonance imaging (micro-MRI) and bilateral hippocampal proton nuclear magnetic resonance spectroscopy (1H-NMRS) in vivo at 7.0 T. A neurochemical assessment of metabolites in the hippocampus was evaluated and analyzed.

Results: 1. Rats COPD model were successfully established by passive cigarette smoking plus intratracheal instillation of LPS. 2. Compared with the normal group, the mean value of Cho/Cr is significantly altered in the bilateral hippocampal of COPD rat model (p < 0.05), but The mean value of NAA/Cr without difference (p>0.05).

Conclusion: Our results demonstrate that the metabolism is significantly altered in rats COPD model bilateral hippocampal, it is possibly one of pathophysiological factors for the COPD complicated with chronic brain damage.

P3585
COPD: Different psycholology status (PS) in the patients with different co-morbidity rate
Kateryna Gashynova. Internal Medicine, DSMA, Dnipropetrovsk, Ukraine

Aim: To evaluate whether and in which extent co-morbidity have influence on the PS in patients with COPD.

Study population: 120 outpatient men with COPD, stage III made the study sample. Exclusion criteria were 1) mental diseases; 2) presence of acute infections.

Methods: For the evaluation of the PS the depression (by Zung scale), the anxiety (by Ch.D. Spilberger questionnaire) and the vegetative lability (by VELA test) were studied in all patients. Co-morbidity rate was established during patient's medical documentation.

Results: In accordance with co-morbidity rate all patients were divided on three groups (GR): GR I without any co-morbidity condition, GR II – with I-2 and GR III – with more than 3 co-morbid conditions. All groups were similar regarding to age and smoking status. One or more abnormalities in PS were found in 2 (10.5%) patients of Group I, in 63 (74.11%) – of Group II and 13 (81.25%) persons in Group III. The data of psychological tests are presented in the table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Depression (M±m)</th>
<th>Personal anxiety (M±m)</th>
<th>Situational anxiety (M±m)</th>
<th>Vegetative lability (M±m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=19)</td>
<td>28.7±9.1</td>
<td>25.1±3.9</td>
<td>22.4±1.4</td>
<td>22.4±4.5</td>
</tr>
<tr>
<td>II (n=85)</td>
<td>40.4±4.5</td>
<td>39.4±3.4</td>
<td>21.1±1.6</td>
<td>20.5±4.3</td>
</tr>
<tr>
<td>III (n=16)</td>
<td>63.3±10.5*</td>
<td>43.6±3.5*</td>
<td>23.4±0.3</td>
<td>38.1±2.5*</td>
</tr>
</tbody>
</table>

*p (III-I)<0.05; p* (III-II)<0.05; p* (II-I)<0.02; p (III-ID) =0.001; p* (II-ID) =0.004

Conclusions: Co-morbid condition significantly impair psychollogy status in patients with COPD, and the most significant changes concerns depression, personal anxiety and vegetative lability level.

P3586
Arterial hypertension (AH) and endothelial function (EF) in patients with COPD
Tetyana Pertseva, Natalia Yefimova, Kateryna Gashynova. Internal Medicine, DSMA, Dnipropetrovsk, Ukraine

Objective: To investigate the influence of co-morbid AH at the EF in patients with COPD.

Materials and methods: A total of 41 men with stable COPD stages I-was observed. Mean age – 61.4±1.41 years, mean disease duration – 15.5±0.38 years.

Group I consisted of patients without concomitant AH – 21 patients, Group II – with AH – 20 patients. Pulmonary function was evaluated by spiograph MasterLab (Jeger, Germany), endotelin-1 plasma level (ET-1) – by reagents "Diamab 86" (DRG, USA), the concentration of exhaled NO (FeNO) – by Niox Mini (Aerocine, Sweden), SaO2 – by pulse oxymeter (NOMIN, USA).

Results: Both groups were comparable. In Group II the concentration of FeNO was significantly higher than in group I (14.8±1.59 ppb and 9.75±1.41 ppb, respectively (p <0.05)). In group II the level of ET-1 was similar to data in group I (0.81±0.02 mg/ml and 0.78±0.03, respectively (p > 0.05)). In group II the level of ET-I significantly correlated with SaO2 (r = -0.38, p = 0.025). We didn’t found any significant correlation between EF and airflow obstruction.

Conclusions: High concentration of FeNO in COPD patients indicates the presence of more pronounced endothelial dysfunction in patients with concomitant AH, plasma levels of ET-I increases with an increase in hypoxia in patients with COPD only if there is concomitant AH.

No significant correlation in exhaled air and plasma levels of ET-I in patients with COPD, regardless of the presence of an accompanying AH, does not correlate with indices of airflow obstruction.

P3587
The impact of comorbidities related to BMI in COPD patients
Carlos Cabrera Lopez1, Jorge Zagaceta 2, Claudia Cote 3, Miguel Divo4, Juan Carlos Cabrera5, Carlos Mira6, Damian Latorre 6, Juan Taboada7, Amador del Olmo8, Santiago Carrizo2.

Aims: The impact of comorbidities related to BMI in COPD patients with chronic obstructive pulmonary disease (COPD rat model (p<0.05), but The mean value of NAA/Cr without difference (p>0.05). In group II the level of ET-I significantly correlated with SaO2 (r = -0.38, p = 0.025). We didn’t found any significant correlation between EF and airflow obstruction.

Conclusions: High concentration of FeNO in COPD patients indicates the presence of more pronounced endothelial dysfunction in patients with concomitant AH, plasma levels of ET-I increases with an increase in hypoxia in patients with COPD only if there is concomitant AH.

No significant correlation in exhaled air and plasma levels of ET-I in patients with COPD, regardless of the presence of an accompanying AH, does not correlate with indices of airflow obstruction.

Introduction: In COPD patients a higher BMI is associated with better survival (the obesity paradox). The mechanism of this paradox is not well understood. We explored whether different co-morbidities related to survival in patients with different BMI.

Methods: We followed 1646 COPD patients of the BODE cohort. A total of 80 comorbidities were systematically recorded. Comorbidities prevalence and association with mortality was explored using Cox proportional hazard stratified by BMI in four groups (≤ 21, 22-29, 30-35, ≥ 36 kg/m²).

Results: COPD patients with BMI ≥ 36 had significantly more comorbidities than the other groups but they had lower mortality, better FEV1 and lower BODE.

No specific co-morbidities had an independent association with mortality in this group whereas they did in the other subsets. Patients with a BMI between 22 and 35 had the most number of comorbidities associated with death.

Conclusions: In COPD, obese patients (BMI≥36) have a better survival than non-obese patients, in spite of having more co-morbidities. In these obese patients there was no co-morbidity that was significantly and independently associated with mortality.

<table>
<thead>
<tr>
<th>BMI grouping</th>
<th>BODE ≤ 21</th>
<th>BMD 22-29</th>
<th>BMI 30-35</th>
<th>BMI ≥ 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>n total</td>
<td>251</td>
<td>924</td>
<td>176</td>
<td>113</td>
</tr>
<tr>
<td>n alive</td>
<td>107 (42.6%)</td>
<td>588 (63%)</td>
<td>255 (86%)</td>
<td>87 (76%)</td>
</tr>
<tr>
<td>n dead</td>
<td>143 (57.3%)</td>
<td>336 (37%)</td>
<td>121 (14%)</td>
<td>28 (24%)</td>
</tr>
<tr>
<td>FeNO (median and SD)</td>
<td>65±10.35</td>
<td>64±9.49</td>
<td>65±6.6</td>
<td>63±5.48</td>
</tr>
<tr>
<td>PEV1 (median and SD)</td>
<td>35±20.5</td>
<td>47±19.9</td>
<td>50±18.5</td>
<td>51±17.3</td>
</tr>
<tr>
<td>BODE (median and SD)</td>
<td>66.27</td>
<td>6±2.8</td>
<td>3±2.4</td>
<td>3±2.35</td>
</tr>
</tbody>
</table>

Average # of comorbidities
Alive (median and SD) | 4±3.3 | 6±2.8 | 5±3.4 | 7±4.6 |
Died (median and SD) | 6±3.6 | 6±3.6 | 6±3.6 | 8±5.4 |

ANOVA 0.048 <0.0001 0.21 0.047

TUESDAY, SEPTEMBER 27TH 2011

WITHDRAWN
P3588
Fibrinogen, health status and hospitalization in patients with moderate to severe COPD
Vladimir Hodges1, Blagoi Marinov2, Roman Kalinov1, Lyudmila Vladimirova-Kitova1, Fedya Nikolov1, Stefan Kostianev3
1Pulmonary Medicine Clinic, Medical University of Plovdiv, Plovdiv, Bulgaria; 2Cardiology Clinic, Medical University of Plovdiv, Plovdiv, Bulgaria; 3Cardiology Clinic, Medical University of Plovdiv, Plovdiv, Bulgaria

Background: There is evidence that COPD is a systemic illness. Serum biomarkers have been associated with clinically relevant variables.

Aim: To investigate the relationships between the blood level of fibrinogen and large group of clinical and functional parameters.

Patients and methods: Twenty-nine stable COPD patients (age [yr] = 63.4±6.8, FEV1% = 37±11%, BODE index = 3.7±1.8) were enrolled in the study. Pulmonary function tests, blood-gas measurements; echocardiography, brain naturotic peptide (BNP), 6-minute walking test (6MWT) and cardiovascular exercise test (CPET) on a treadmill were performed. In addition, health status was evaluated by SGRQ (St George’s Respiratory Questionnaire) and CAT (COPD assessment test).

The presence of fibrinoegen, independently of the need for antibiotic treatment and oral/intravenous corticosteroids (OICS) in the 12 months prior to evaluation were recorded.

Results: The mean value of fibrinogen was 3.06±0.8 [g/L]. Fibrinogen correlated significantly with health status - SGRQ (r = 0.49, p = 0.008), CAT (r = 0.44, p = 0.016) and hospitalizations (r = 0.50, p = 0.006), and OICS application (r = -0.48, p = 0.012). Differentiation of patients by value of fibrinogen (> 3 g/L) was discriminated them with respect to last year hospitalisations (1.8±1.9 vs 0.6±1.3; p < 0.05). A general linear model analysis was performed for SGRQ and hospitalisations and the following equations were derived: SGRQ = 146.7-25.6*OICS+5.68*FIBR–15.83*KCO (r=0.918; r²=0.843, p<0.05).

Conclusion: Blood level of fibrinogen was related to health status and hospitalization in patients with moderate to severe COPD.

P3589
Ego defense mechanisms in COPD: Impact on health-related quality of life and dyspnoea severity
Saulo C. Albuquerque1, Eduardo R. Carvalho1, Rebeca S. Lopes1, Igor S. Marques1, Danielle S. Macêdo2, Eanes D. Pereira3, Thomas N. Hyphantis3, Andrea P. Carvalho1,2
1Clinical Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil; 2Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, Ceará, Brazil; 3Department of Psychiatry, University of Ioannina, Ioannina, Greece

Purpose: To assess chronic obstructive pulmonary disorder (COPD) patients’ defensive mechanisms and to test whether specific ego defense mechanisms are associated with health-related quality of life (HRoL) and self-reported dyspnoea severity.

Methods: In a cross-sectional study, we assessed in 80 patients with COPD and 80 age and gender matched healthy participants, psychological distress (Hospital Anxiety and Depression Scale) and defense mechanisms/styles (Defense Style Questionnaire). Patients had their HRoQL evaluated with the St George’s Respiratory Questionnaire and underwent a comprehensive clinical evaluation with determination of functional parameters and dyspnoea severity.

Results: COPD patients presented higher scores in undoing, acting out, autistic fantasy, denial and splitting defenses compared to healthy-controls. Overall, patients showed a more immature (p=0.001) and/or neurotic (p=0.006) defensive profile. Higher scores of denial (p=0.001) and denial and undoing (p=0.032) defenses were associated with poorer HRQoL, independently of the anticipated significant associations of clinical and psychological distress variables with impaired HRQoL. Somatization was strongly independently associated with more severe self-reported dyspnoea.

Conclusions: COPD patients exhibit a relatively immature and neurotic defensive profile. Pneumologists and consultation-liaison psychiatrists should consider the patients’ underlying personality structure, especially somatization tendencies, since it is independently associated with HRQoL and dyspnoea severity.

P3590
Heart rate variability during the night in chronic obstructive pulmonary disease
Riccardo Inchingolo1, Giuseppe Maria Corbo1, Gregory Angelo Sgueglia2, Gaetano Lana2, Salvatore Valenti1
1Pulmonary Medicine, Università Cattolica del Sacro Cuore, Roma, Italy; 2Cardiovascular Diseases, Università Cattolica del Sacro Cuore, Roma, Italy

Patients with chronic obstructive pulmonary disease (COPD) could have a lower oxygen saturation during the night compared to the day-time and it could affect autonomic modulation of heart rate. We studied the behaviour of heart rate variability (HRV) during the day-time versus the night in COPD patients. 30 stable outpatients were recruited and classified by BODE index. A 24 h electrocardiographic Holter recording and a transcutaneous measurement of oxygen saturation were performed at the same time. Lung function was also measured. Statistical analysis was made by linear regression.

According to BODE index, 13 patients belonged to first group (BODE 1=0-2), 8 to second group (BODE 2=3-4) whereas 9 were included in the third group (BODE 3=5-10).

During the night, we observed, compared to the day-time, a significant increase of both normal-to-normal (NN) intervals (i.e. a reduction of heart rate, 831 vs 720 msec, p<0.000), and Standard Deviation of all RR intervals (SDNN, 94.3 vs 85.5 msec, p<0.03), and High Frequency band (HF; 14.86 vs 10.97 msec p=0.0004) with reduction of ratio of low frequency to HF band (LF/HF ratio, 1.54 vs 1.96 p<0.09). Mean oxyhaemoglobin saturation (SpO2) during the night was directly and significantly related to both SDNN (p=0.0018) and HF (p<0.057). Subjects with mean SpO2 lower than 90% showed lower SDNN (60 vs 100 msec, p<0.012) and lower HF (8.2 vs 16.2 msec, p=0.04). LF/HF ratio was found unrelated to mean SpO2 during the night, but a close inverse relationship was found with RV/TLC ratio (p<0.005).

Our data demonstrated that in COPD patients both level of oxygen saturation of haemoglobin and impairment of static lung volumes could affect the cardiac autonomic modulation.

P3591
Changes in bronchial mucous membrane depending on the stage of COPD (I, II)
Tetyana Pertseva, Igor Ivakh, Oxana Plekhanova
Internal Medicine Department, Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine

Aim: To determine immune-histochemical characteristics of bronchial mucous membrane depending on the stage COPD (I, II).

Study population and methods: 78 patients (pts) (mean age 54.2±2.4 years) with COPD were divided on two groups (Gr); Gr I – 32 pts with 1 stage (22 male), Gr II – 46 pts with II stage (31 male). Bronchoscopy with consequent histology sampling, and assessing by microscopy and immunohistochemistry research was done for all pts. The following indexes were evaluated: Ki-67 (reflect proliferative potential and activity of epithelial regeneration); Cytokeratin 8 (Ck8) (as a marker of glandular epithelium proliferation); 34EpIE12 expression (for estimation of squamous metaplasia).

Results: Both groups were similar regarding to age, gender and duration of disease. Results of immunohistochemistry present in table 1.

In Group I in all pts there were intensive positive membrane reactions with Ck 8 in ciliary and basal epithelial cells and absence of reaction with cytokeratin 34EpIE12. But there were not any microscopically signs of hyperplasia. In Group II all pts took place intensive positive membrane and cytoplasmatic reaction with Ck 8 in goblet and basal cells with morphologically signs of hyperplasia. Besides, in every sample there were foci with high Ck 34EpIE12 expression in basal cells.

Conclusion: 1. Pts with COPD, stage I have significantly higher potential for the bronchial epithelial cells’ regeneration in comparison with COPD, stage II. Co-expression of both Ck 8 and 34EpIE12 in COPD pts, stage II allows to suppose high risk of irreversible metaplasia in bronchial epithelium.

P3592
GERD and anxiety in patients with severe COPD
Sherif Alyayed
Internal Medicine, NJCH, Jedda, Saudi Arabia

Objectives: To detect the impact of anxiety on shaping the prevalence of gastro-intestinal reflux disease (GERD) in patients with severe chronic obstructive pulmonary disease (COPD).

Methods: We examined the prevalence of symptomatic GERD, using the Vignieri score, in 29 male patients with COPD. Esophageal 24 h pH monitoring was used to document the diagnosis of GERD in symptomatic group. Beck Anxiety inventory was used to detect the impact of anxiety on expressing GERD symptoms.

Results: Reflux disease symptoms were recorded in eighteen patients of the studied group (62%). GERD was diagnosed, based on esophageal 24 h pH monitoring, in only 11 patients of those who expressing symptoms of GERD. Mean of Anxiety score was correlated significantly with the number and frequency of symptom presentation in patient with symptoms of GERD reflecting the attribute of different symptoms of anxiety to the GERD syndrom. Also Anxiety scores correlated positively with time (total) PH reflecting the effect of anxiety on the severity of GERD syndrom.

Conclusion: Patients with severe chronic obstructive pulmonary disease have a high prevalence of symptomatic gastro-oesophageal reflux. However True GERD was documented in a fewer number of them. Psychological factors, such as anxiety and somatization may play a role, particularly in those patients without esophageal inflammation.
Introduction: Multiple endocrinological disorders are induced by COPD through hypoxemia, hypercapnia, systemic inflammation and glucocorticoid administration; thyroid structural and functional derangements are amongst them.

Objectives: Our aims were to find out if COPD is a risk factor for thyroid disorders and what type of thyroid derangement is more specific to different COPD stages.

Methods: 2 groups of patients were assessed for age, gender, environment, smoking, alcohol intake, diabetes, dyslipidemia and thyroid disorder (autoimmune thyroid disease, nodular and nodulocystic goitre). First group was composed by non-COPD pts (N = 148, 19 M/128%, 129 F/78% mean age 61.33, SD 10.21) and the second one by COPD pts (N = 137, 79 M/57.66%, 58 F/42.33%, mean age 64.34, SD 10.94). COPD pts were staged according to GOLD criteria in stage I and II/IIb and the male to female ratio was 1.23 (p = 0.055). The relative risk to develop a thyroid disorder 0.123 (p < 0.01). There is also a low relative risk of 1.043 (p = 0.05, 95% CI 0.24-0.83) for the COPD stage I pts to develop autoimmune thyroid disease.

Conclusions: COPD pts have a relative low risk to develop a thyroid disorder. In COPD stage I, with more individuals in this study, the risk was found higher for patients affected by thyroid disorder. Because growing in no gaseometric anomalies nor glucocorticoid interventions, we suggest that systemic inflammation is the most probable link; the inflammatory blood markers analysis should be taken into consideration for the next studies.

Nutritional abnormalities are frequently occurring systemic complication of COPD. They often determine functional capacity, health status and mortality of patients (pts). However, causes and mechanisms of weight loss are still under investigation.

Aim: The aim of study was to reveal influence of systemic inflammation on the nutritional status in COPD.

Study population and methods: 69 men with stable COPD (Stage II-III) were surveyed. Plasma C-reactive protein (CRP), spirometry, measurement of body mass index (BMI) and Fat Free Body Mass (FFBM) by means of bioelectric impedance analysis were performed for all pts.

Results: In accordance with CRP level all pts were divided on two groups: Group I – pts with CRP < 2.87 mg/l; Group II – pts with CRP > 2.87 mg/l.

Results of nutritive status examination present in table 1.

Results: There is a significant correlation between COPD and the presence of a thyroid disorder 0.123 (p < 0.01). There is also a low relative risk of 1.043 (p = 0.05, 95% CI 0.24-0.83) for the COPD stage I pts to develop autoimmune thyroid disease.

Conclusions: COPD pts have a relative low risk to develop a thyroid disorder. In COPD stage I, with more individuals in this study, the risk was found higher for patients affected by thyroid disorder. Because growing in no gaseometric anomalies nor glucocorticoid interventions, we suggest that systemic inflammation is the most probable link; the inflammatory blood markers analysis should be taken into consideration for the next studies.

**Reference:**

Laura Ciobanu1, Vasile Maciuc2, Roxana Costan3, Andreea Gorga4, Paula Alina Bobica5, Stefania Cofman6, Internal Medicine, University of Medicine and Pharmacy “Gr T Popa”, Iasi, Romania; 2Scientific Research and Experimental Technique, “Gr T Popa” University of Agricultural Sciences and Veterinary Medicine, Iasi, Romania; 3Endocrinology, County Emergency Clinical Hospital “Gr T Popa”, Iasi, Romania; 4Clinical Section of Respiratory Rehabilitation, Clinical Hospital of Rehabilitation, Iasi, Romania

**Methodology:**

**Introduction:** Multiple endocrinological disorders are induced by COPD through hypoxemia, hypercapnia, systemic inflammation and glucocorticoid administration; thyroid structural and functional derangements are amongst them.

**Objectives:** Our aims were to find out if COPD is a risk factor for thyroid disorders.

**Methods:** 2 groups of patients were assessed for age, gender, environment, smoking, alcohol intake, diabetes, dyslipidemia and thyroid disorder (autoimmune thyroid disease, nodular and nodulocystic goitre). First group was composed by non-COPD pts (N = 148, 19 M/128%, 129 F/78% mean age 61.33, SD 10.21) and the second one by COPD pts (N = 137, 79 M/57.66%, 58 F/42.33%, mean age 64.34, SD 10.94). COPD pts were staged according to GOLD criteria in stage I and II/IIb and the male to female ratio was 1.23 (p = 0.055). The relative risk to develop a thyroid disorder 0.123 (p < 0.01). There is also a low relative risk of 1.043 (p = 0.05, 95% CI 0.24-0.83) for the COPD stage I pts to develop autoimmune thyroid disease.

**Conclusions:** COPD pts have a relative low risk to develop a thyroid disorder. In COPD stage I, with more individuals in this study, the risk was found higher for patients affected by thyroid disorder. Because growing in no gaseometric anomalies nor glucocorticoid interventions, we suggest that systemic inflammation is the most probable link; the inflammatory blood markers analysis should be taken into consideration for the next studies.
There were no relationships with genotyping and exacerbation frequency for any of the polymorphisms. There was a seasonal difference in viD levels but this was the same for all polymorphisms; all $p<0.05$.

Conclusions: FokI, BsmI and TaqI VDR polymorphisms are not associated with exacerbation frequency and do not affect viD levels in COPD.

**P3598**

Is there any correlation between apoptosis of the cells from bronchoalveolar lavage fluid (BALF) and the progression of chronic obstructive pulmonary disease (COPD)?

Agata Nowicka1, Halina Batura-Gabryel 1, Mariusz Kaczmarek 2, Jan Sikora 2, Krysztof Siewieckik 1, Anna Czyz 3.

**Background:** It has been already well known that neutrophilic inflammation, oxidative stress and protease/antiprotease imbalance play a significant role in the pathogenesis of COPD. In recent years some data were published, showing that also apoptosis may be one of the processes concerned in the pathogenesis of this disorder.

**Objectives:** We presumed that apoptosis of the cells (granulocytes, lymphocytes, macrophages) from COPD patients' bronchoalveolar lavage fluid increases along with the decline of FEV1 (forced expiratory capacity in 1 second).

**Methods:** 19 patients (16 men and 3 women), smokers or former smokers, diagnosed with COPD (stages 2-4) were enrolled into the study. The mean age was 64.5±27.83. In all subjects spirometry after the inhalation of beta-2-agonist was performed, to confirm the diagnosis of COPD according to GOLD criteria and to estimate FEV1. BALF during fibroptic bronchoscopy was taken in all patients. We used annexin V to assess apoptosis of the cells concerned in BAL fluid. (BD Biosciences, Annexin V - FITC Apoptosis Detection Kit I)

**Results:** The median FEV1 was 38.6%. Only the patients with advanced COPD were enrolled into the study (max FEV1 55.3%, min FEV1 15.3%). In the group of patients with FEV1 lower than 38.6% median for apoptosis was 4% (0.59%), in the group with FEV1 higher than 38.6% median for apoptosis was 5% (3.16%). No correlation between FEV1 and apoptosis of the cells concerned in COPD patients BALF was found ($p=0.74$).

**Conclusions:** Our data suggest that there is no correlation between apoptosis and the progression of COPD.

**P3599**

The regional distribution of body fat mass (BFM) in men with chronic obstructive pulmonary disease (COPD)

Aliaksandr Makarevich, Sviatlana Lemiasheuskaya.

**Introduction:** COPD is associated with abnormal body composition and weight loss.

**Aim:** To evaluate the relationships between BFM distribution and lung function in men during COPD progression.

**Methods:** We used dual-energy X-ray absorptiometry for an analyze of body composition, the regional distribution of BFM as well as fat mass ratios of Android/Gynoid (A/G) and Arms+Legs/trunk. COPD pts (aged 40-69 yrs) were divided into the 3 groups according to disease severity: the 1st was made of 14 men (GOLD I stage; mean age 56 yrs; FEV1 78%; BMI 27 kg/m2, smokers 66%), the 2nd - 43 pts (GOLD II stage; mean age 57; FEV1 63%; BMI 28 kg/m2, smokers 84%), the 3rd - 20 pts (GOLD III stage; mean age 66%, packs/years 20). The A/G ratio was significantly lower in 3rd group vs. the control ($p<0.05$).

**Conclusions:** BFM redistribution (decrease A/G ratio and increase Arms+Leg/trunk ratio) take place in the course of COPD progression.

**P3600**

Pulmonary features of autosomal dominant hyper-IgE syndrome (AD HIES)

Hanna Dmewska1, Edyta Heropolińska2, Barbara Pietrucha3, Ewa Bernatowska4.

AD HIES is characterized by recurrent severe pulmonary infections, pneumatoceles, eczema, staphylococcal abscesses, mucocutaneous candidiasis, abnormalities of bone and connective tissue and elevated serum IgE. Mutations in signal transducer and activator of transcription 3 (STAT3) have been recently found to account for most cases.

**Aim:** The aim of the study is to present clinical phenotype of AD HIES.

**Materials and methods:** A group of 22 HIES pts were genetically analyzed. The mutations in STAT3 were confirmed in 7 AD HIES pts, presented here. Recurrent and severe pulmonary infections were found in all pts except one (pt 7) at various time intervals. The typical complications of pneumomas were the formation of pulmonary cysts and abscesses. Long term complications included pneumatocele and bronchopleural fistulae. In several cases lobectomy was performed. The structural abnormalities were then sites of fungal and Gram (-) infection.

**Results:**

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>P</th>
<th>L</th>
<th>A</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. JJ M 25 / *6 c.1110-2A&gt;G</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. DD M 22 / *3 1909G&gt;A-V673M</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. LT M 20 / *11 1909G&gt;A-V673M</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4. KZ F 15 / *2 1144C&gt;T-R302W</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5. WI F 14 / *5 1145G&gt;A-R302Q</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6. MK M 11 / *3 2141C&gt;G-T714A</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7. MB M 3 / *1 1145G&gt;A-R302Q</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Age at diagnosis (yr). P: pneumonia; LA: lung abscess; L: lobeectomy; PC: pneumatocele.

**Conclusions:** 1. Early recognition of the HIES enables to introduce the right kind of therapy. 2. Pneumomas should be treated aggressively to try to prevent parenchymal damage. 3. If pneumatocele and bronchiectasis are present, antimicrobial prophylaxis covering Gram (+) bacteria and fungi is needed.

**P3601**

Is quantitative HRCT related to diagnostic yield of fiberoptic bronchoscopy in sarcoidosis?

Branislav Gvozdenovic1, Violeta Vucinic-Mihailovic2, Jelena Marinkovic3.

**Aim:** To evaluate the diagnostic yield of fiberoptic bronchoscopy (FOB) modalities and its relation with quantitative findings with high resolution computerized tomography (HRCT).

**Materials and methods:** Sixty patients that consists of 19 males and 41 females with the mean age of 43 diagnosed with sarcoidosis with complete records of HRCT were retrospectively recruited for a time period of Feb 2000 to Jan 2010. HRCT scans were retrospectively assessed in random order by an experienced observer without knowledge of the bronchoscopy result or lung function tests. The diagnostic yield of transbronchial biopsy (TBB) was 43.6. Although it did not reach statistical significance, the lobar HRCT score in the sampled lobe was associated with a positive TBB result. Bronchial mucosa appearance was significantly related with positive mucosal biopsy (MB). The diagnostic yield of MB was 45.4. In general patient population however in patients with abnormal mucosa this rate was increased up to 70%.

**Results:** The diagnostic yield of fiberoptic bronchoscopic (FOB) modalities and its relation with quantitative findings with high resolution computerized tomography (HRCT). 64 patients that consists of 19 males and 45 females with the mean age of 43 diagnosed with sarcoidosis with complete records of HRCT were retrospectively recruited for a time period of Feb 2000 to Jan 2010. HRCT scans were retrospectively assessed in random order by an experienced observer without knowledge of the bronchoscopy result or lung function tests. The diagnostic yield of transbronchial biopsy (TBB) was 43.6. Although it did not reach statistical significance, the lobar HRCT score in the sampled lobe was associated with a positive TBB result. Bronchial mucosa appearance was significantly related with positive mucosal biopsy (MB). The diagnostic yield of MB was 45.4. In general patient population however in patients with abnormal mucosa this rate was increased up to 70%.

**Conclusions:** 1. Early recognition of the HIES enables to introduce the right kind of therapy. 2. Pneumomas should be treated aggressively to try to prevent parenchymal damage. 3. If pneumatocele and bronchiectasis are present, antimicrobial prophylaxis covering Gram (+) bacteria and fungi is needed.

**P3602**

Importance of fatness measurement in sarcoidosis patients

Branislav Gvozdenovic1, Violeta Vucinic-Mihailovic2, Jelena Marinkovic3.

**Aim:** To evaluate the diagnostic yield of fiberoptic bronchoscopy (FOB) modalities and its relation with quantitative findings with high resolution computerized tomography (HRCT). 64 patients that consists of 19 males and 45 females with the mean age of 43 diagnosed with sarcoidosis with complete records of HRCT were retrospectively recruited for a time period of Feb 2000 to Jan 2010. HRCT scans were retrospectively assessed in random order by an experienced observer without knowledge of the bronchoscopy result or lung function tests. The diagnostic yield of transbronchial biopsy (TBB) was 43.6. Although it did not reach statistical significance, the lobar HRCT score in the sampled lobe was associated with a positive TBB result. Bronchial mucosa appearance was significantly related with positive mucosal biopsy (MB). The diagnostic yield of MB was 45.4. In general patient population however in patients with abnormal mucosa this rate was increased up to 70%.

**Conclusions:** 1. Early recognition of the HIES enables to introduce the right kind of therapy. 2. Pneumomas should be treated aggressively to try to prevent parenchymal damage. 3. If pneumatocele and bronchiectasis are present, antimicrobial prophylaxis covering Gram (+) bacteria and fungi is needed.
Fatigue is recognized as one of the most prominent symptoms in sarcoidosis patients. In the cross-sectional study in 189 biopsy proven sarcoidosis patients (138 female) with average disease duration of 14.6 years, we evaluated the relationship between the fatigue severity and their health status and pulmonary function tests. Fatigue was measured by standardized Fatigue Scale, which contains 14 items, with four response options (the higher the score, the more severe fatigue). Scale distinguishes between fatigue, physical fatigue, and it is also possible to calculate a total fatigue score. Two health status questionnaires were administered: respiratory specific – the St Georges Respiratory Questionnaire (SGRQ) and generic – the 15D Total SGRQ and 15D scores, as well as the scores for individual domains of SGRQ, were calculated for each patient. The pulmonary function was determined by means of spirometry and body-plethysmography.

Introduction: Sarcoidosis is a systemic granulomatous disease with predominant manifestation in the lungs, however other organs can be involved, including heart, what is potentially life-threatening. The aim of this study was to evaluate the incidence of cardiac involvement in sarcoidosis patients diagnosed or followed up in 1st and 3rd Lung Diseases Departments of National TB & Lung Diseases Research Institute in Warsaw.

Method: Retrospective analysis of database discharged patients with the final diagnosis of sarcoidosis (D86). The analysis covered the period from January 2008 to October 2010. Diagnosis of cardiac sarcoidosis was verified according to Modified Guidelines for Diagnosis of Cardiac Sarcoidosis based on the Study Report on Diffuse Pulmonary Diseases: From the Japan Ministry of Health and Welfare, 1992 and 1993 modifications 2006.

Results: 933 sarcoidosis patients were seen in two departments in the almost 3 years period. Multorgan sarcoidosis (D86.8) was detected in 102 cases (10.9%). The cardiac involvement was found only in 30 patients of this group, which was 3.2% of the entire group. There were 19 males (63%) and 11 females (37%), 5 cases in stage I, 25 in stage II. The mean age was 45.5 ± 12.6 years (range: 28-74). The time from the first diagnosis of sarcoidosis to detection of heart involvement was 10 months (median, CI 90% range 0 to 6.4 years).

Conclusion: Cardiac sarcoidosis in our own material was diagnosed in the similar percentage as in previously published data. According to post mortem diagnosis data from literature diagnosis of this form of the disease still remains a significant clinical problem.

Primary thoracic amyloidosis: Rare disease and hard diagnosis

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Amyloidosis is a disease caused by extracellular deposition of complex protein-polysaccharide in a β-pleated configuration within soft tissues. Primary thoracic deposition of amyloid is scars. To explore the different thoracic manifestations of primary thoracic amyloidosis (PTA) and its diagnosis difficulty, we retrospectively analyzed cases of PTA hospitalized in our department between 2007 to 2009. PTA (AL-type) diagnosis was confirmed by pathological study in all cases. All patients were investigated by chest x ray, fiberbroncoscopy and chest and abdominal CT scan.

Our study concerned 5, 63 years mean aged (34-77) men. PTA discovery was secondary to respiratory symptoms in 4 cases and fortuitous in 1 case. Amyloidosis was systemic in 1 case and localized to the thorax in 4 cases: 1 involved pleura, 2 involved mediastinal lymph nodes, 2 the bronchial tree and 2 the lung parenchyma. An association of 2 different thoracic localization was noted in 2 patients. The average time of diagnosis was 4 months, based on open lung biopsy in 2 cases, mediastinal lymph node biopsy in 2 cases and transbronchic lung biopsy in 1 case. Respiratory lung function was normal in 3 patients. Amyloidosis was complicated by chronic respiratory failure in 1 patient and severe obstructive disease in 1 patient. Treatment consisted in colchicin with a stable trend (1 case), systemic corticosteroids with clinical deterioration (2 cases), lung resection (2 cases). One patient disappeared during follow up. PTA diagnosis is often delayed. This is due in part to the localized features of amyloidosis, non specific symptoms and frequent misdiagnosis.
and the patient underwent urgent coronary angiography, which revealed entirely normal coronary arteries but an abnormal left ventriculography. There was marked LV apical hypokinesis and ballooning. Cardiac MRI supported the suspicion of Takotsubo’s cardiomyopathy.

**Discussion:** Takotsubo’s cardiomyopathy is a cause of cardiac chest pain and troponin release, accounting for up to 2% of ST-elevation myocardial infarction (MI). The important measure of the burden of related morbidity and mortality is the occurrence of ADRs. Preventive measures should be taken to minimize the occurrence of ADRs.

**Conclusions:** Our study shows that ADRs are an important cause of morbidity in our hospital. Disease prevalence and drug use patterns in our hospital differ markedly from those of generally recognized ones. These differences affect the frequency and nature of ADRs. Preventive measures should be taken to minimize the occurrence of ADRs.

**P3607**

**Multiple pulmonary nodules in a patient with polyarteritis nodosa**

Genevieve Chailous, Isabelle Cutteix, Claude Portier. Pulmonology, Centre Hospitalier Université de Montreal, Montreal, QC, Canada

We are reporting the case of a 58-year-old woman, investigated for a 6 weeks history of abdominal pain, nausea, shortness of breath and weight loss of 25 pounds. Her medical history was otherwise insignificant. Upon presentation, the woman was febrile at 38.5 C, had tachycardia, low blood pressure despite aggressive volume repletion, leukocytosis and acute renal failure. A CT scan of the thorax and abdomen showed multiple nodules within the thyroid gland, the lungs, liver and kidney parenchyma. The patient was put on broad-spectrum antibiotics and anti-fungal medication. BAL (bronchoscopy) and all cultures remained negative. A screen for vasculitis and virus were negative. A liver biopsy showed areas of necrosis due to ischemic insults. Later, the patient developed gastrointestinal bleeding. An angiographic embolization meant to be curative turned out to be diagnostic. We discovered many small aneurysms affecting the mesenteric, hepatic, gastroipiplic and the bleeding site from an ileal branch was successfully embolized. A vasculitic origin (PAN) to the patient’s symptoms was underlined by a positive ANA test, high levels of IL-6, elevated creatinine; characteristic angiographic abnormalities. The patient rapidly recovered with IV steroids and cyclophosphamide.

Polyarteritis nodosa is known to affect multiple organs, but the lung. Very few cases of polyarteritis nodosa involving the lung have been reported. Necropsy reports also described pulmonary fibrosis. Cases of acute interstitial pneumonia, BOOP and alveolar hemorrhage have been described. To our knowledge, it would be the first case of micromodular lung involvement in association to PAN. This case raises awareness to a possible pulmonary involvement in PAN.

**P3608**

**Sarcoidosis patient: Do we need to perform plethysmography when spirometry and DLCO were done?**

Piotr Boros1, Magdalena Murawsicz-Boros2, Philip Quanger1, Paul Erricht1, Stefan Wesolewski1, 1 Lung Function Lab, National TB & Lung Diseases Research Institute, Warsaw, Poland; 2Department of Pulmonary Diseases, Erasmus Medical Centre, Erasmus University, Rotterdam, Netherlands; 3College of Public Health, University of Arizona, Tucson, AZ, United States

**Introduction:** Plethysmographic measurement of total lung capacity (TLCple) is the gold standard for measuring lung volumes. Gas dilution methods are considered less accurate in patients with substantial airway obstruction and take more time. TLCple is usually done in patients suspected of having an interstitial lung disease (ILD) and the test includes measurement of alveolar volume (VA).

**Aim of study:** To compare TLCple with TLCVA in a large group of sarcoidosis patients in different stages of the disease.

**Methods:** Data from 830 consecutive sarcoidosis patients (223 in stage I, 486 in stage II, and 121 in stage III). All tests met 2005 ATS/ERS FTT technique and quality guidelines. TLCple was calculated as the sum of VA and dead space.

**Results:** TLCple was larger than TLCVA by a mean of 0.18 L (95%CI: 0.15; 0.20) and 2.8% (95%CI: 2.3; 3.3). TLCple was normal (above the 5th percentile) in 772 patients (93%) by TLCple, and in 762 cases (92%) by TLCVA. Sensitivity of the TLCple for a low TLCple was 83% and specificity 97%, so NPV was 99% and PPV 71%. The AUC by ROC analysis was 0.90. Airway obstruction was present in only 12% of the patients, but their TLCple was significantly lower than their TLCVA when compared to those without airway obstruction (0.39 L ± 0.39 vs. 0.15 L ± 0.39). In this subgroup, the sensitivity of TLCVA was only 50% and specificity 96%, so NPV was 96% but PPV only 33%. The differences of TLCple and TLCVA were correlated with FEV1/FVC ratio.

**Conclusions:** A normal TLCple rules out a low TLCVA with a high degree of certainty in patients with sarcoidosis, but a low TLCple does not confirm a low TLCple in patients with airway obstruction.

**P3609**

**Adverse drug reactions in a pulmonary teaching hospital: Incidence, pattern, seriousness, and preventability**

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**Introduction:** Detection of adverse drug reactions (ADRs) in hospitals provides important measure of drug related morbidity in the healthcare system. Studies have shown that between 1.7% and 25.1% of hospital inpatients experience an ADR during their hospitalization.

**Aim of study:** This aimed study focused on incidence, pattern, seriousness, and preventability of hospital-acquired ADRs, in medical wards of a pulmonary teaching hospital in Iran.

**Methods:** Clinical pharmacist residents were trained to report all suspected ADRs through ADR-reporting yellow forms. The incidence, pattern, seriousness, and preventability of the reported ADRs were analysed.

**Results:** During the period of 24 months, for 16125 patients, 312 ADR reports were reported. The most frequently reported reactions were due to anti- infective agents (26.54%). Ceftriaxone accounted for the highest number of the reported ADRs among anti-infective agents. The gastro-intestinal system was the most frequently affected system (21.78% of all reactions). Eighteen percent of the ADRs were reported as serious reactions. Fifty of the ADRs were classified as preventable.

**Conclusions:** Our study shows that ADRs are an important cause of morbidity in our hospital. Disease prevalence and drug use patterns in our hospital differ markedly from those of generally recognized ones. These differences affect the frequency and nature of ADRs. Preventive measures should be taken to minimize the occurrence of ADRs.

**P3610**

**Importance of cardiac biomarkers in the evaluation of acute pulmonary thromboembolism severity, mortality and complicated clinical course**

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**Background:** Severity of pulmonary thromboembolism (PTE) is related to the determination of early mortality risk rather than distribution and the load of trombus. To determine the risk evaluation biomarkers level have important roles than echocardiography, alternatively.

**Aim:** Investigation of the usefulness of biomarkers in the determination of 3 months complicated clinical course (CCC) and mortality, and also acute PTE risk level.

**Material and methods:** Demographic characteristics, history, clinical findings, risk factors, additional diseases, hemodynamic symptoms of 47 patients (22M, 25F) with objectively documented diagnosis of PTE, were recorded. Before PTE treatment, serum and plasma samples were kept to measure the levels of D-Dimer, cTnT, cTnI, NT-ProBNP, HAPFR and GDF-15. Patients were followed for 3 months for complication and mortality.

**Results:** NT-proBNP levels were similar in submassive and nonsmassive groups but they were significantly higher in massive group when compared to nonmassive group (p=0.031). Mortality was present in 9 patients. When all the deaths caused are predicted by D-Dimer, HAPFR, NT-ProBNP and GDF-15, deaths caused by PTE were only predicted by D-Dimer, HAPFR and GDF-15 levels. NT-proBNP and GDF-15 valuables were predicted the complications (p< 0.05).

**Conclusions:** This biomarkers used in this study had no significant role in the differentiation of nonmassive and submassive groups. However, NT-proBNP and GDF-15 have been shown that these biomarkers would be beneficial for mortality and CCC, in prediction of 3 months.

**P3611**

**Is utility of D-Dimer test undermined because of overuse in routine clinical practice?**

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**Introduction:** In suspected VTE a low pre-test probability and negative D-Dimer is associated with risk of VTE < 2%. However d-dimer is raised in many conditions and utilities and depends on VTE prevalence in population tested (9.5-19% in validation studies). Purpose of study was to assess utility of d-dimer testing in routine practise.

**Methods:** Case records of patients d-dimer tested in A&E or on admission to hospital were reviewed. Data included: clinical features, admission diagnosis and pre-test probability if recorded. Investigators estimated VTE-risk, calculated post-test probability of VTE and impact on imaging

**Results:** 96 cases included; 52 female, mean (SD) age 61yrs. Symptoms: chest pain 44.5%; leg pain/swelling 28%; dyspnea 17%, syncope 7.5%, other 3%. Admission diagnosis: VTE likely 10%, VTE possible 57%, other diagnosis 33%. Pre-test probability done in 23. Investigator pre-test VTE-risk: High (H) 9%, Moderate (M) 20%, Low (L) 33%. Very Low (V) 38%. D-Dimer positive 43% (H 100%, M 64%, L 44%, V 41%; p<0.05). VTE-Imaging if d-dimer +ve (VTE-risk M, L, V) 41% in 11.3% OR 5.1 (9.15) p=0.001. Prevalence of VTE was 2.3% (sensitivity 1.0, specificity 0.58; negative likelihood ratio 0.0-1.1).
Pre and post-test probability of VTE if negative d-dimer: VTE-risk M-H pre-8%, post-<1%; VTE-risk V-L pre-<2%, post-<1%.

Conclusion: Prevalence of VTE in patients D-dimer tested in clinical practice is much lower than in validation studies. Both high risk and very low risk patients with alternative diagnoses are often tested. If VTE risk is very low a negative d-dimer test makes little difference to post-test probability of VTE but positive tests lead to unnecessary imaging.

Aims: To assess compliance and safety of our hospital pathway for out-patient management of suspected PE.

Methods: We studied a prospective cohort of patients with suspected PE managed as outpatients using LMWH from the day of presentation until either the diagnosis of PE was excluded or confirmed. We analysed patients referred to ambulatory care clinic with suspected PE from June 2009 till June 2010. 42 patients met the inclusion criteria. All patients were reviewed in clinic after a V/Q scan or CTPA.

Table 1. Clinical presentations

<table>
<thead>
<tr>
<th>Presenting complaint</th>
<th>Total (n=42)</th>
<th>PE diagnosed (n=16)</th>
<th>PE excluded (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Pain</td>
<td>32 (76%)</td>
<td>13 (81%)</td>
<td>19 (73%)</td>
<td></td>
</tr>
<tr>
<td>SOB</td>
<td>26 (62%)</td>
<td>10 (63%)</td>
<td>16 (61%)</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>3 (7%)</td>
<td>1 (6%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Leg swelling/pain</td>
<td>11 (26%)</td>
<td>5 (31%)</td>
<td>6 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

Results: 16 (38%) patients were diagnosed with PE. Average time taken for PE to be diagnosed or excluded was 56 hours. There were no deaths or complications recorded from either PE or LMWH. No significant differences in clinical and physiological parameters were noted except for systolic BP (p 0.043).

Table 2. Results

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Respiratory Rate</th>
<th>PO2 (Pa)</th>
<th>PCO2 (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>136</td>
<td>80</td>
<td>16</td>
<td>97</td>
<td>4.65</td>
</tr>
<tr>
<td>79</td>
<td>130</td>
<td>81</td>
<td>17</td>
<td>97</td>
<td>4.55</td>
</tr>
<tr>
<td>82</td>
<td>141</td>
<td>80</td>
<td>16</td>
<td>97</td>
<td>4.78</td>
</tr>
<tr>
<td>0.836</td>
<td>0.043</td>
<td>0.717</td>
<td>0.709</td>
<td>0.046</td>
<td>0.508</td>
</tr>
</tbody>
</table>

Conclusion: It’s probably safe to investigate and treat suspected PE as outpatient in selected clinically stable patients. Larger multi-centre randomised controlled trials are needed to confirm this finding.

P3615

Lung function tests in patients suffering from chronic kidney insufficiency before and after hemodialysis.

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Most frequently encountered alteration of lung function in patients on hemodialysis is existence of restricted ventilation and consequently insufficiency caused by hypervolemia. Various studies examined changes in lung micro circulation that follow hemodialysis and it is argued that they may cause lung fibrosis and even calcification of alveolar septa. The objective of this study is a comparison of the relative results of pulmonary function tests before and after hemodialysis treatment.

Using Chest-microspirom HI 601 apparatus, we have monitored 35 patients whose average age was 57 years. The diagnostic tools consisted of chest roentgenograms, laboratory tests, clinical examinations and pulmonary function tests (FVC, FEV1 and PEF). Our results indicate a statistically significant increase in FVC (p < 0.05) and FEV1 (p < 0.05) before and after hemodialysis.

Conclusion: Patients receiving hemodialysis treatment have prominent fluid re-tenion in lung spaces. In this situations spirometry performed before and after hemodialysis can be used as a valid diagnostic approach in determining patient conditions.

P3616

Effect of bicarbonate versus acetate hemodialysis on respiratory functions in chronic renal failure patients.

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Dialyzer filter can cause activation of complement and release of anaphylatoxines which can have a deteriorating effect on respiratory system.

Aim of the work: To compare the effect of bicarbonate versus acetate haemodialysis on the pulmonary function test and blood gas parameters.

Material and methods: Cross sectional study of fifty chronic renal failure patients on regular haemodialysis without history of chronic pulmonary disease were randomly selected for dialysis either by bicarbonate or acetate dialysate twenty five each with same machine and duration of dialysis. Evaluation thorough medical history and determination of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and maximal mid-expiratory flow rate (I50% 25%-75%). Arterial oxygen tension (PaO2), PH, carbon dioxide tensions (PaCO2), bicarbonate (HCO3) and potassium were analyzed with a blood gas analyzer.

Results: No significant difference in symptoms before and after dialysis in both groups. Improvement of pulmonary function test was significant in bicarbonate
Results: Among the studied patients, 55% had pulmonary complications in the ESRD maintained on regular hemodialysis. Spirometric measures, before and after arterial blood gases, radiological study of chest and heart and spirometric study are important causes of morbidity and mortality in patients with ESRD and infection is the second leading cause of death among them.

Aim: To study pleuro-pulmonary changes and complications among patients with ESRD maintained on regular hemodialysis.

Patients and methods: The current study included 20 patients with ESRD on regular hemodialysis for at least 6 months. For every patient, clinical, laboratory, arterial blood gases, radiological study of chest and heart and spirometric study were done.

Results: Among the studied patients, 55% had pulmonary complications in the form of pulmonary infections, pleural effusion, pulmonary edema or hypoxemia during the course of hemodialysis. Spirometric measures, before and after hemodialysis, showed no significant improvement of VC, FVC, FEV1/FVC, MMV wherewith improvement in FEF25-75% and PEFR was significant. Significant hypoxemia occurred during hemodialysis. Significant improvement in pHa, pCO2 and HCO3 occurred during and after hemodialysis.

Conclusion: Patients with ESRD treated with hemodialysis must be considered at high risk for the development of lethal pulmonary complications. Regular hemodialysis improves arterial blood gases parameters and some pulmonary function measurements.

P3618 Morphological features of the endobronchial microcirculation of nephropathic patients
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Pneumofibrosis is one of the respiratory aftereffects developing at late stages of chronic kidney disease (CKD). The research was aimed at revealing the microhemocirculatory disturbances role in the course of bronchopulmonary aftereffects development for CKD patients.

Methods: The endobronchial biopsy was applied to 48 CKD patients at the point of 1cm distally aside from the right lung’s proximal bronchus spur. The ultrathin sections were analyzed, using the Tecnai G2 Spirit TWIN electron microscope (of the “FEI Company” - Netherlands) after its preliminary staining by the uranyl acetate and the lead citrate.

Results: The normal plan of bronchi mucosa structure is revealed in 16.6% of cases, mainly at CKD initial stages. 25.4% of CKD 2nd and 3rd stage patients had epithelium initial planocellular metaplasia, sometimes with the bronchi submucosa connective tissue edema. In 50% of the cases dystrophy and epithelium metaplasia combined with the microcirculatory bed reduction. At the later stages of the disease the number of the elastic fibers increased which surrounded the spasmatic blood capillaries and dilated veins. 19.4% of the patients at the fifth CKD stage showed atrophy of the epithelium against the expressed submucosa sclerotic changes. Here one could observe distinct damages of endothelial cells containing numerous vacuoles in the cytoplasm, sometimes they protruded into the vessel lumen.

The conclusion: Due to various factors the CKD leads to the structural reorganization of the microhemocirculatory bed which then causes the fabric hypoxia, atrophy of the bronchus mucosa and occurrence of the expressed sclerotic processes in the submucosal layer of the bronchial tree.

P3619 Bronchiolitis obliterans as a first manifestation of rheumatoid arthritis - Case report
Simona Luca, Ali Zakia. Chest Department, Faculty of Medicine, Minoufiya University, Shebin El Kom, Minoufiya Governorate, Egypt

Introduction: Rheumatoid arthritis (RA) is the most common connective tissue disease associated with bronchiolitis obliterans (OB). OB is a clinico-pathologic entity of bronchiolar inflammation which reflects the injury of the small airways and presents symptoms and signs of small airways obstruction. OB can go as a first manifestation of RA in 10–20% of patients. Case presentation: A 37-year-old woman, non-smoker presented to our clinic accusing: MRC III dyspnea and bronchorexia and suddenly it developed an obstructive lung disease without any reasonable explanation. Clinical, physiological and radiologic features suggested OB (squeaks and crickles on auscultation, functional evidence of OB). HRCT scan features consisted mostly of indirect signs of bronchiolitis, with a mosaic pattern reflecting air trapping, bronchial wall thickening, centrilobular emphysema, areas of ground-glass attenuation. She also had extra-respiratory symptoms-asthma and weight loss (5 percent in 2 months). 3 months after, she developed seropositive RA and a elevate serum rheumatoid factor was found, but with no clinical evidence of active rheumatoid disease. All of these findings suggests that the OB was secondary to a rheumatoid process. Oral corticosteroids, associated with immunosuppressive treatment and inhaled bronchodilators was initiated, but without any clinical and functional improvement.

Conclusions: This case is atypical since usually the diagnosis of RA precedes respiratory symptoms in 88% of cases. In our patient the bronchiolitis obliterans was the initial manifestation of rheumatoid arthritis, attributable to rheumatoid arthritis.

396. What do individuals know about their disease? Educational needs, the psychological impact of chronic respiratory disease and health-related quality of life

P3620 Late-breaking abstract: Older COPD patients’ requirements for eMonitoring and eCoaching: A user-centered study
Jose de Lintelo1, Mari van de Dijck2, Dienst Behandeling en Begeleiding/Home Care, Division for Treatment and Support, Carint Reggeland Group, Hengelo, Netherlands; 2Expertise Centre of Health, Social Care and Technology, Saxson University of Applied Sciences, Enschede, Netherlands

Introduction: COPD patients can have increased indepdence, when adequately supported by appropriate technology, with eHealth opening new opportunities for self-management at home.

Aims: The aims were to explore the requirements of older COPD patients, for an effective eHealth home care system, and through this to promote self-management, reduce health care use and increase quality of life.

Methods: A qualitative user-centred design, combining focus groups with a scenario-based approach, was used to elicit key criteria for the home care system. Data were collected in two workshops involving patients aged 63 to 83 (n=17). Most had moderate COPD (GOLD II-III- IV); all experienced dyspnoea and restrictions in their activities of daily living.

Results: Participants have the prerequisites for a (mobile) eHealth system and in general want to use their mobile phones. Participants provided specific needs, wishes and preconditions for eHealth, in physical, cognitive/emotional and social areas; reporting daily activities and problems in which they could use the help. They underlined the importance of technology stimulating patients to maintain and extend their existing abilities.

Conclusions: The user-centred design approach enabled patients to identify for themselves, their key requirements for an eHealth system. They wanted support for self-management, to increase confidence in their own abilities and their sense of security. The integration of eMonitoring and eCoaching can support patients to maintain and improve their independence and quality of life at home. An “eCOPD” system is being designed based on the outcomes from this study.

P3621 Assessing the educational component of pulmonary rehabilitation with the lung information needs questionnaire (LINQ)
Ria Fowler, Karen Ingram, Claire Nolan, Pipas Marns, Amy Clark, Michael Polkey, William Man. Harefield Pulmonary Rehabilitation Team and Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, Harefield, Middlesex, United Kingdom

Introduction: Educational sessions are an integral part of pulmonary rehabilitation (PR) programs but there are few tools to assess their impact. The Lung Information Needs Questionnaire (LINQ) is a patient reported and designed to assess the information needed to understand lung diseases and to maximise self-management skills (Hyland et al 2006). A decreased score indicates less information requirements. We hypothesised that the LINQ is sensitive to change after a PR program and provides additional information to tests of exercise capacity and health status.

Method: We prospectively measured the LINQ, the self-report Chronic Respiratory Disease Questionnaire (CRDQ-SR), Hospital Anxiety & Depression score (HAD) and incremental shuttle walk (ISW) in 217 patients before and after an 8-week outpatient PR program. 11 patients, who declined the outpatient PR pro-
Conclusion: Patients with COPD entering PR have a heterogeneous level of knowledge considering COPD. Therefore, individualized educational programs should be considered to increase patients’ knowledge and, in turn, improve self-management.

P3624

Fatigue components in COPD patients and controls using the FACIT-F scale; data from ECLIPSE study

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Background: Fatigue is a complex multi-dimensional phenomenon and its dimensionality in COPD and controls has not been adequately investigated. We aimed to examine the dimensions as well as the reliability and validity of the FACIT-F scale.

Methods: At baseline, 2107 COPD patients and 576 control subjects with normal lung function from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE; SCON010406, NCT00292552) completed the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale. The FACIT-F was readministered to 1621 patients and 515 controls after 3 years. We used the principal components analysis (PCA) for structurally examining the 13 items FACIT-F.

Results: The 13 items were loaded into two and three interpretable dimensions in COPD and controls, respectively. In COPD, FACIT had high internal consistency (Cronbach’s α = 0.92) and long-term reproducibility (r = 0.68, p < 0.001). In the two-factor solution, the two components of fatigue in COPD correlated well with the total score of the scale (r = 0.59 and 0.99, p < 0.001 for both). FACIT had significant convergent validity when associated with BODE, SGRQ and MRC dyspnoea scores (r = 0.42, 0.7 and 0.48, respectively, p < 0.001 for all). FACIT had good discriminating validity; patients who walked <350m in 6 minute walk test as well as depressed patients were significantly more fatigued than those who walked ≥350m or who were not depressed (p < 0.001).

Conclusion: The FACIT-F is a short and easily administered scale with good validity and reliability in COPD. It may be possible to measure different fatigue components with this scale.

P3625

Long-term changes in the COPD assessment test (CAT) after pulmonary rehabilitation

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Introduction: The COPD assessment test (CAT) is a recently introduced, validated, patient-completed quality of life instrument that is immediately responsive to pulmonary rehabilitation (PR) [1]. The long-term effects of PR on the CAT, and whether these changes relate to more established health status instruments, are not known. We hypothesised that long-term improvements in CAT (reduced score) following PR would correlate with improvements in the self-report Chronic Respiratory Disease Questionnaire (CRDQ-SR) total score (increased score).

Method: The CAT and CRDQ-SR were recorded in 39 COPD patients before (T1), immediately after (T2) and 6-months after (T3) an 8 week outpatient PR program. On completion of the PR course, patients were offered individualised exercise advice and goal-setting, but no formal supervised exercise training. Changes in

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Table 1

<table>
<thead>
<tr>
<th>Statement</th>
<th>Correct answers (%)</th>
<th>Incorrect answers (%)</th>
<th>I do not know (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviation of “COPD”</td>
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<td>33</td>
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<tr>
<td>Meaning of exacerbation</td>
<td>26</td>
<td>19</td>
<td>55</td>
</tr>
<tr>
<td>Effect of PR on pulmonary function</td>
<td>22</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Influence of physical exercise on the lungs</td>
<td>60</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Typical symptoms of COPD</td>
<td>23</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>Meaning of self-management</td>
<td>61</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

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Farmaceutici SpA. Visit Chiesi Farmaceutici SpA, at Stand D.30
CAT and CRDQ-SR were compared from T1 to T2 and from T1 to T3. Spearman's
rank correlation was used to assess the relationship between changes in CAT
and CRDQ-SR between T1 and T2 and T1 and T3.
Results: Mean (SD) age was 72 (7) and FEV1% predicted was 47 (19%). CAT
and CRDQ-SR scores at T2 and T3 were significantly improved compared to
corresponding scores at T1.
T1-T3 changes in CAT correlated significantly with changes in CRDQ-SR: r =
-0.40; p<0.01.
Conclusion: Following PR, short and long-term changes in CAT score mirror the
CRDQ-SR score.
References:
P3626
CAT (COPD assessment test) as outcome parameter of pulmonary
rehabilitation and in COPD
Konrad Schultze1, Oliver Gohl1, Dragan Stojanovic1, Michael Wittmann1,
Juliane Rudnik1, Monika Schwarze2, 3. 1 Bereich Pneumologie, Klinik Bad
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Medizinische Hochschule Hannover, Hannover, Germany
Background: The COPD Assessment Test (CAT) is a newly developed question-
naire for COPD-patients. The CAT is designed to measure the impact of COPD
on a patient’s life, and how this changes over the time. The test contains 8 items.
Methods: In a prospective observational study 124 patients with COPD were
included, 71.6% male, 42.5% with GOLD Stage 1-2, 26.6% with stage 3, 28.2%
with stage 4. Mean FEV1 was 1.661. Outcome parameters were 6-MWD, FEV1,
MRC-dyspnoea scale and in addition the CAT was used for the first time in
Germany as an outcome parameter in PR.
Results: Mean CAT score at admission (T0) was 21.97±6.49 and at discharge
from PR (T1) 18.94±6.56 (p<0.0001); CAT scores from 20-30 indicate a high
impact of COPD on patient’s life, as shown at admission. At discharge the average
CAT score was reduced out a medium impact, as a defined range from 10-20 points.
The minimal clinically important difference (MCID) for CAT is supposed to be
a change of 2 points. In 56.6% of the patients the CAT score decreased for at
least 4 points and therefore MCID was achieved. The average improvement was
a reduction of 3.03 points. Improvement occurred in all items of the CAT, but
the item with the highest impact was breathlessness on effort.
Conclusions: In this prospective observational study all COPD-patients were
included, regardless of comorbidity or exacerbations. In spite of these circumstances
there was a statistically significant and clinically relevant improvement. More than
50% of the patients improved the CAT score for at least 2 points (MCID). The test
was successful with our patients without relevant problems and so, since July 2010,
the CAT is used as a routine outcome parameter in our PR program.
P3627
Changes in the CRQ, CAT and updated BODE index by pulmonary
rehabilitation
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H'Schwindi, Switzerland Pneumology, Berner Reha Zentrum, H'Schwindi,
Switzerland
Background: It is unclear to which extent a standardised in-hospital rehabilitation
program may change the new COPD assessment test (CAT) score and the updated
BODE index in very severe COPD patients.
Method: In a prospective study we assessed the CRQ, CAT and updated BODE
scores in severe and very-severe COPD patients before and after attending a
multidisciplinary in-hospital rehabilitation program of a approximately 3
week’s duration. The assessment comprised in addition sociodemographic and
health data. According to the initial BODE Index and due to statistical reasons we formed two
BODE severity groups; group one with 0-7 points and group two with 8-15 points.
Results: 315 patients attending a pulmonary rehabilitation program were assessed
between first of July and end of December 2010. Thereof 132 patients presented
with severe or very-severe COPD. The mean age was 69.2 years, exactly one
third female, mean duration of stay 19.9 days.
I. Both groups showed a significant improvement for all four CRQ domains. Only
for the domain dyspnea the improvement was significant smaller for patients with
a higher BODE score (second group).
II. The CAT score showed a similar significant improvement in both groups
(reduction of 4.5 and 5 points respectively)
III. Also the updated BODE Index showed a significant reduction in both groups,
however, this reduction was significant less for the second group.
Conclusion: The CAT and the updated BODE Index might both provide a valid
assessment for changes in an inpatient pulmonary rehabilitation program for severe
and very-severe COPD patients.
P3628
Determinants of health-related quality of life in patients with severe COPD
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Medicine, Maastricht University Medical Centre, Maastricht, Netherlands
Introduction: Clinical presentation of COPD patients is very heterogeneous. Pa-
tients with a comparable degree of airflow limitation present with a wide range
in health-related quality of life (HRQOL). This study investigates determinants of
HRQOL in severe COPD patients.
Methods: Assessment data were extracted from the records of 1562 COPD pa-
tients referred for pulmonary rehabilitation. HRQOL was assessed by St. George’s
Respiratory Questionnaire (SGRQ). Data were divided into quadrants of FEV1
and total SGRQ score.
Results: Compared to patients with FEV1<50% and SGRQ<50, those with
SGRQ≥50 are characterized by lower BMI, better exercise performance, fewer
exacerbations in last year, lower depression (HADS-D) and anxiety (HADS-A)
scores and less dyspnea (MRC). In stepwise multiple regression analysis, MRC,
HADS_A and HADS_D. 6MWD and number of exacerbations in last year were
independent predictors for HRQOL.
Discussion: Clinical, physiological and psychological factors determine HRQOL
in severe COPD. These factors must be taken into account in the disease manage-
ment of these patients.
P3629
Evaluation of quality of life instruments for COPD care and research
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Utrecht, Netherlands; 2Department of Rehabilitation, Nursing Science & Sports,
University Medical Center Utrecht, Utrecht, Netherlands
Background: Quality of Life (QOL) measurements to quantify the impact in
Chronic Obstructive Pulmonary Disease (COPD) with a standardized method has
become important in the last decades. A variety of QOL instruments are available.
To facilitate decision making with regard to an appropriate QOL instrument in
COPD care and research, a systematic review was performed.
Objective: To identify and evaluate content and psychometric properties of cur-
cently available QOL instruments in COPD care and research.
Method: A systematic literature search was done. Based on criteria, 2 investiga-
tors independently identified eligible studies. Methodological quality and data on
psychometric properties were assessed by using the Consensus based Standards
for selection of health status Measurement Instruments (Mohrnik et al. J Clin
Results: 56 Studies, 11 disease-specific and 10 generic QOL instruments are identi-
fied. Methodological studies’ quality is mostly rated fair. In 50 studies theoretically
derived hypotheses are not described. In 34 studies confirmatory factor analysis
was not performed. Measurement properties are in general positive. Chronic Res-
piratory Questionnaire has slightly better results than generic measures: hypothesis
testing correlation r=0.5, Chronbach’s α=0.7, Intra Class Correlation (ICC) 0.5-0.9
The new COPD assessment test α=0.88, ICC= 0.8. Disease-specific instruments
hold domains like dyspnea and activity. Social activity, emotional status, anxiety
and pain are mostly included in generic instruments.
Conclusion: Since both disease-specific and generic domains are important in
measurement of QOL in COPD patients, we recommend to use at least two QOL
instruments covering as many domains as possible.
P3630
Coping style and health status in COPD patients entering pulmonary
rehabilitation
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Medicine, Maastricht University Medical Centre, Maastricht, Netherlands
Background: Mood status contributes to an impaired health status in patients
with COPD. Coping style may also be related to health status. Our objective was to assess disease-specific health status in COPD patients entering pulmonary rehabilitation after stratification for coping style and mood status.

Methods: Coping styles were studied in 698 COPD patients entering PR (60% men; mean (SD) age: 64 (10) yrs; FEV1: 48 (18% pred.) using the Urutch Coping List. The current analysis is limited to passive coping style. Disease-specific health status (St. George’s Respiratory Questionnaire (SGRQ)), and symptoms of anxiety (HADS-A) and depression (HADS-D) were recorded.

Results: Mean (SD) SGRQ total score was 54 (17) pts. Clinically relevant symptoms (HADS-A > 10 pts) and depression (HADS-D > 10 pts) were reported by 30% and 23% of the patients, respectively. Low level of passive coping style was reported by 18% of the patients; medium level by 39% and high level by 43% of the patients. In patients with HADS-A or HADS-D > 10 pts. SGRQ total score was higher for patients with a high passive coping style than for patients with a low or medium level passive coping style. In patients with HADS-D > 10 pts, differences did not reach statistical significance.

Conclusions: The level of passive coping style may have a relationship with health status in COPD patients after stratification for symptoms of anxiety and/or depression.

P3631
Relationship between quality of life, exercise capacity and disease severity in patients with chronic obstructive pulmonary disease
Michelle M.C. Le Cheminant 1, Gillian Austin 2, Camilla Bastu 2, Thida Win 1.

The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) is a new, simple questionnaire designed to evaluate quality of life in COPD patients. In contrast to more complex assessment tools (such as St. George’s Respiratory Questionnaire), no studies have evaluated its relationship with other disease severity markers in COPD such as walk test.

This study investigated the relationship between CAT score and markers of disease severity in COPD, including forced expiratory volume in 1 second (FEV1), endurance shuttle walk test (ESWT) and incremental shuttle walk test (ISWT).

Fifty patients with a known diagnosis of COPD (male: female ratio 22:28, mean age 68 ± 13.3 years, mean FEV1 16.9 ± 20.3% of predicted) were evaluated using spirometry, ESWT and ISWT. Quality of life was assessed using CAT. Mean ISWT was 182 ± 124 metres and mean ESWT was 6.9 ± 6 minutes.

CAT score correlated negatively with ESWT (r = -0.40, p < 0.01) and ISWT (r = -0.30, p < 0.05). There was no significant correlation with FEV1 in this study population. However, it is very interesting that CAT score is inversely related to exercise capacity. As the disease gets more severe, quality of life worsens (higher score on CAT), but becomes less able to do things (lower ESWT/ISWT).

Although this concept is logical, it was not described previously.

Our study showed that CAT represents a useful instrument to evaluate disease impact in COPD, when interpreted alongside complementary diagnostic information. It would be really interesting to see the relationship of CAT and other parameters in COPD, when interpreted alongside complementary diagnostic information.

P3632
Quality of life evaluation in patients with alpha1-antitripsin deficiency: A 3-year prospective study
Mauro Carone 1, Gisella Bruletti 2, Enrica Bertella 2, Gianluigi Balestroni 3, Gisella Bruletti 2, Enrica Bertella 2, Gianluigi Balestroni 3, Mauro Carone 1, Gisella Bruletti 2, Enrica Bertella 2, Gianluigi Balestroni 3, Gisella Bruletti 2, Enrica Bertella 2, Gianluigi Balestroni 3.

AATD is associated to pulmonary disease, mainly COPD. In comparison to COPDs without AATD, pts with AATD and COPD present an accelerated decline of lung function in conjunction to other COPD characteristics: frequent exacerbations, disabling symptoms (dysnea and phlegm), reduction in exercise capacity and daily life activities. These pts, therefore, frequently have respiratory disability. However, their impairment appears in a relatively younger age in comparison to COPD.

Aim of the study: Our aim was to evaluate pts’ QoL in relation to the use/not use of augmentation therapy.

Material and methods: We performed a 3 year prospective study in 32 pts (mean age 54±10 yrs; M/F 19/13; FEV1 48±24% predicted). The St George’s Respiratory Questionnaire (SGRQ) and the EuroQol (EQ-5D) were administered at baseline and yearly for three years. According to their spirometric impairment, patients were stratified in Group T vs. treated with weekly infusions of AAT (25 µg), and Group NT. i.e. not treated (7 pts).

Results: After 3 years, the decrease in FEV1 in Group T was 125 ml (4%), whereas in Group NT was 610 ml (41%); p<0.02.

SGRQ changes over three years were significantly different in the two groups. Group T showed a 7.8 unit improvement, whereas in Group NT QoL worsened by 7.9 units (p < 0.04 over time between groups).

Conversely, the EQ-5D did not detect any change in health status between the two groups or over time.

Conclusion: These data show that AATD associated with COPD determines a decrease in patients’ health status that may be slowed down by augmentation therapy. The improvement in health status in T Group can be detected by the SGRQ but not the EQ-5D.

P3633
Effect of gender on exercise capacity and hospital anxiety and depression scale (HADS score following pulmonary rehabilitation
Debapriya Datta 1, Richard ZaWallack 2.

The objective of this study was to determine whether gender impacts change in outcome following pulmonary rehabilitation (PR). The records of 241 COPD patients who underwent a hospital-based, 8-week outpatient PR programme were reviewed. All patients received upper and lower extremity exercise training and smoking management. Pre- and post-outcome measures were: 6-minute walk distance (6MWD), self-reported Chronic Respiratory Questionnaire (CRQ-SR), unsupervised armlifts/minute (UAL), Hospital Anxiety and Depression scale for anxiety (HADS-A) and depression (HADS-D), before and after PR. Mean age was 69.1±7 years; 49% were females; mean FEV1 was 49% of predicted. Outcomes measures are shown in the following table:

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Pre &amp; Post-PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Pre-6MWD (meters)</td>
<td>281±90</td>
</tr>
<tr>
<td>Post-6MWD (meters)</td>
<td>318±97</td>
</tr>
<tr>
<td>Pre-UALs (per min)</td>
<td>47±5.17</td>
</tr>
<tr>
<td>Post-UALs (per min)</td>
<td>59±6.18</td>
</tr>
<tr>
<td>Pre-CRQ (units)</td>
<td>4±2.09</td>
</tr>
<tr>
<td>Post-CRQ (units)</td>
<td>4±0.86</td>
</tr>
<tr>
<td>Pre-HADS-A</td>
<td>5±3.3</td>
</tr>
<tr>
<td>Post-HADS-A</td>
<td>4±2.29</td>
</tr>
<tr>
<td>Pre-HADS-D</td>
<td>5±3.3</td>
</tr>
<tr>
<td>Post-HADS-D</td>
<td>4±2.6</td>
</tr>
</tbody>
</table>

Patients in both genders showed significant improvement in all outcome measures. Change in UALs were similar in both genders (p=0.8); females showed greater increase in 6MWD (p=0.01) and CRQ-SR score (p=0.07). Pre-PR HADS-A scores were significantly higher in females (p=0.0009). Females showed greater reduction in HADS-D scores following PR (p=0.02). These data indicate that female COPD patients show greater improvement in outcome areas of exercise capacity, depression and quality of life following PR.

P3634
Pulmonary rehabilitation, COPD assessment test and smoking cessation at smokers with COPD
Paraschiva Postolache 1,2, Octavian Poteciu 2,3, Ingrid Olga Merisaua 2, Luminita Calin 4, Liliana Chelaru 5, Oana Cristina Arghir 6, Daniela Husanu 7.

1Internal Medicine and Pulmonology, “Gr T. Popa” University of Medicine and Pharmacy, Iasi, Romania; 2Pulmonology Rehabilitation Clinic, Rehabilitation Clinical Hospital, iasi, Romania; 3Intensive Care, “Gr. T. Popa” University Clinical Hospital, iasi, Romania; 4Pulmonology Clinic, “Gr. T. Popa” University, Faculty of Medicine, Constanta, Romania

The objective was to compare the improvement of quality of life (QoL) between smokers with chronic obstructive pulmonary disease (COPD) who completed a PR program complementary of the smoking cessation treatment and those who received usual treatment.

Methods: Inclusion criteria were: evidence of COPD according to GOLD standards; an initial HRCT > 2 cm and an initial COPD Assessment Test (CAT) completed by every patient. From 437 smokers with COPD (GOLD stages II-III) only 113 patients were enrolled in a 12 weeks supervised PR program, complementary the smoking cessation treatment (the PR group), and 324 smokers received the treatment for COPD and for stop smoking, monitored as well for 12 weeks (non-PR group). All patients completed the CAT questionnaire at the beginning and at the end of the determined period.

Results: Initially, CAT scores varied between 26-38 without any difference between the PR group and the other patients. At the end of the period, the CAT scores in the PR group were between 7-16 comparing to the non-PR group where
CAT scores shown little improvements since the beginning of the treatment, with values between 20-26, additionally to smoking cessation failure at an important number of non-PR members (45.96%) than the PR group (16.81%). There were reported as well higher rates of long-term abstinence in the patients adherent to PR than the other group.

**Conclusions:** Although current smokers are often expected to have a small PR adherence, COPD smokers who completed the PR presented important QoL, improvements, better CAT score than COPD smokers usually treated. Moreover, a better PR adherence seems to be related with higher rates of sustained long term abstinence.

**P3635**

Factors predicting clinically improved health status in COPD patients after pulmonary rehabilitation

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**Background:** Although pulmonary rehabilitation has proven to be effective in enhancing health status (HS) in COPD patients (Lacasse et al, Cochrane Database Syst Rev 2006; 4), characteristics of those who have the largest potential for HS improvements after rehabilitation are less studied. This knowledge may be useful for physicians’ referral practice.

**Aims:** The aim of the study was to investigate the influence of lung function on a clinical improved health status after rehabilitation adjusted for gender, age, and co-morbidity. Since the association between lung function and health status in COPD patients is usually low (Jones, PW, Thorax 2001; 56: 880-887), we hypothesized no influence of lung function on the post rehabilitation outcome.

**Methods:** A longitudinal study of 136 consecutive male and female patients attending 4 weeks inpatient rehabilitation, aged 40+ and with COPD I-IV. Lung function was assessed by spirometric tests and health status by the St.George’s Respiratory Questionnaire. The influence of independent variables on HS was assessed through logistic regression analyses.

**Results:** Patients with minor disease (FEV1 ≥50% predicted) were more likely to achieve clinically improved health status after rehabilitation than patients with major disease (FEV1 < 50% predicted) (OR 4.2, 95% CI 1.9-9.3, p=0.001), with stronger effect for female than for male patients (OR 7.1, 95% CI 1.9-39.0, p=0.025).

**Conclusions:** Our findings upgrade the significance of lung function on HS in COPD patients, implicating that referral to pulmonary rehabilitation at an early COPD stage is crucial in order to achieve optimal post rehabilitation effect, especially for female patients.

**P3636**

Abnormal illness behaviour amongst COPD patients entering pulmonary rehabilitation

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**Introduction:** COPD patients present with a mixture of symptoms, some of which may not always be attributable to physical pathology. The degree of the psychological and behavioural component of illness may at times be out of proportion with objective physical pathology. Maladaptive perceptions associated with abnormal illness behaviour (AIB) may have negative consequences for patients’ health outcomes.

**Objectives:** The study aimed to 1) investigate the prevalence and type of AIB present in COPD patients entering pulmonary rehabilitation and 2) evaluate the associations between AIBs, quality of life, mental health and level of disability in COPD patients.

**Method:** A cross-sectional study design was employed. Sixty-nine COPD participants entering a pulmonary rehabilitation program completed the Illness Behaviour Questionnaire (IBQ), Hospital Anxiety and Depression Scale (HADS), Short Form 36 (SF-36) and Chronic Respiratory Questionnaire (CRQ).

**Results:** Correlations indicated that AIB was significantly (p<0.01) associated with anxiety, age, dyspnea and emotional function. Multiple regressions indicated that significant (p<0.01) predictive relationships existed between the Hypochondriasis subscale of the IBQ and anxiety (HADS), dyspnea (CRQ) and mental disability (SF36).

**Conclusion:** AIB is linked with health outcomes amongst COPD patients. Early recognition of AIB allows for the tailoring of pulmonary rehabilitation programs to address perception of illness issues.

**P3637**

Anxiety and affecting factors in pulmonary rehabilitation patients with chronic obstructive pulmonary disease during exacerbation

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**Aims:** To investigate the anxiety prevalence and related factors in COPD patients enrolled in the rehabilitation program during exacerbation.

**Material and methods:** Hospital Anxiety and Depression Scale (HAD) was performed to 75 COPD patients (mean age 69.6±8.8 years). Mean HAD anxiety score was 6.4±5.2.

**Results:** Patients in both groups had similar age, systemic diseases, social features, disease severity, arterial blood gases, walking distance, heart rate, respiratory rate and saturation during the walk test. However, there were significant differences in some variables between two groups.

**Clinical and demographic variables of the COPD patients with HAD anxiety scores <11 and ≥11**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospital Anxiety and Depression Scale</th>
<th>Anxiety Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Hospital Anxiety and Depression Scale</td>
<td>Anxiety Score</td>
</tr>
<tr>
<td>Education years, &lt;8</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>Assistive walking device</td>
<td>41%</td>
<td>14%</td>
</tr>
<tr>
<td>Dyspnea during bathing (VAS-mm)</td>
<td>58.3±35.0</td>
<td>39.1±31.1</td>
</tr>
<tr>
<td>Dyspnea during upper dressing (VAS-mm)</td>
<td>41.1±32.0</td>
<td>25.7±24.7</td>
</tr>
<tr>
<td>LTOT</td>
<td>65%</td>
<td>30%</td>
</tr>
<tr>
<td>FEV1/force (L)</td>
<td>52.6±9.5</td>
<td>55.6±10.8</td>
</tr>
<tr>
<td>6MWT test distance (m)</td>
<td>182.2±53.8</td>
<td>262.8±116.0</td>
</tr>
<tr>
<td>Stopped before 6 minutes</td>
<td>75%</td>
<td>27%</td>
</tr>
<tr>
<td>Dyspnea after walk test ( Borg)</td>
<td>5 ±3.2</td>
<td>3.6±2.9</td>
</tr>
<tr>
<td>Miss-nutritional score</td>
<td>18±4.4</td>
<td>22±2.4</td>
</tr>
</tbody>
</table>

**Conclusion:** Despite similar disease severity and walk tests in both groups, patients with high anxiety scores having higher ratio of the inability to complete walk test, more severe symptoms during the test and ADL made us suggest that anxiety levels restricted their participation in physical activity. We think that appropriate psychiatric approach will increase the rehabilitation gains among patients with high HAD anxiety scores.

**P3638**

The impact of anxiety and depression on outcomes of pulmonary rehabilitation in COPD

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Anxiety and depression are highly prevalent comorbidities in chronic obstructive pulmonary disease (COPD) and related to a negative course of disease. We examined the impact of anxiety and depression on functional performance, dyspnea and quality of life in patients with COPD at start and end of an intensive 3-week outpatient pulmonary rehabilitation program (PR).

Before and after PR, 238 patients with COPD (mean age = 62 years) underwent a 6-minute walking test (6MWT). In addition, anxiety, depression, quality of life and dyspnea at rest, after PR and during activities were measured.

**Results:** The results demonstrate that anxiety and depression are significantly associated with increased dyspnea and reduced functional performance and quality of life in patients with COPD. These negative associations remain stable over the course of PR, even when improvements in most of these outcomes are achieved during PR.

**Conclusion:** The findings underline the clinical importance of diagnosing and treating anxiety and depression in patients with COPD.

**P3639**

Quality of life (QoL) in asthma 1 year after pulmonary rehabilitation (PR)

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**Background:** There are only sparse data on the effectiveness of PR on QoL in
asthma. Therefore we conducted a prospective observational study to determine the effect of a 3 week inpatient-PR on QoL.

Methods: From May to September 2009 all asthma patients of our pulmonary rehabilitation clinic were asked to participate in the study, 201 out of 243 (83%) agreed. 43.2% female, mean age 48.4 y (18-81), SRaw (PaPV) 1.23±0.80 before and 0.88±0.54 after inhalation of a rapid-acting beta-2-agonist (RABA). 59.6% suffered from asthma GINA grade 3-4. Obligate components of PR were patient education, physical training, breathing retraining and psychosocial support. QoL was assayed by using St. George’s Respiratory Questionnaire (SGRQ) and Asthma Quality of Life Questionnaire (AQLQ). Measuring times were the beginning of PR (T0), discharge (T1) and 3 (T2), 6 (T3) and 12 months (T4) post PR. The three latter were delivered by mail. 83.5% (T2), 88% (T3) and 72.6% (T4) of the patients answered.

Results (mean±sd): sgrq total score: T0 38.6±18.3; T1 27.8±17.4; T2 30.9±20.7; T3 32.5±20.7; T4 32.7±20.7. AQLQ[S] score: T0 4.6±1.2; T1 5.5±1.1; T2 5.2±1.3; T3 5.0±1.3; T4 5.0±1.3. FEV1 [l] after RABA: T0 3.10±0.88; T1 3.22±0.80 (p<0.01 versus T0).

Discussion: The reduction of mean SGRQ score and increasing of mean AQLQ score indicate improvement of QoL after PR. Both indicate a great effect at discharge, which diminishes a little after 1 year. The positive effect at discharge was assured by the lung function measurements. After 1 year still 45% (AQLQ) to 55.8% (SGRQ) of the patients have a selfreported benefit.

Conclusion: PR can a resting improvement of QoL in asthmatics at least for one year.

397. Challenges in rehabilitation: some old dilemmas revisited with some solutions?

P3640 Late-breaking abstract: Bi-level positive airway pressure (Bipap) effects on regional distribution of lung ventilation in COPD

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Aim: To assess changes on distribution of lung ventilation before and after Bipap, in patients (pts) with chronic respiratory failure (CRF) due to severe COPD.

Methods: 11 COPD pts (mean age 69.3±7.5), in stable conditions, underwent two successive ventilation scans (V) with a radioabeled aerosol (99mTc nanocolloid albumin, Ventillog, GE). The first ventilation was done using FAI device (Fastera, MPR), and the second one using an adapted nasal mask system (FAZ), which allows evaluation of (V) distribution after Bipap. Clinical symptoms and arterial blood gas analysis were observed before and after treatment. The images of (V) before and after Bipap were quantified by a semi-automatic procedure which divides each lung in 3 regions of interest (ROI): upper, medium and lower lung field to obtain the upper/upper (U/L) ratio. An automatic iso-level ROI procedure enabled radioactivity measurement (counts) of ventilated area (Va 5% and 30%), on the right posterior and on the right lateral lung. A ventilation distribution inhomogeneity index (IHI) was defined as the ratio counts/pixels, calculated on isoROI 5% and 30% (INI 5 and 30%).

Results: A significant reduction of U/L ratio (F=12.12, p<0.02) and of cardiac rate (p=0.01) were accompanied by a significant increment of pO2 (p<0.02) and pH (p<0.001). Ventilated area (Va 5% and 30%) increased, and INI 5 and 30%, decreased, even if both not significantly.

Conclusions: A significant improvement of the physiologic gradient (U/L), an increment of ventilated areas (Va 5%, 30%), and a reduction of regional ventilation inhomogeneity index (INI) are likely underlying the therapeutic effect of the Bipap in COPD.

P3641 Late-breaking abstract: Efficacy of relaxation posture in patients with chronic obstructive pulmonary disease (COPD)

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Background: Relaxation postures are recommended to reduce the work of breath-
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Maintenance of long-term benefits from an outpatient pulmonary rehabilitation programme in COPD

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We evaluated the long term maintenance of benefits of a Pulmonary Rehabilitation programme (PRP) in COPD patients and to establish which patients require frequent repetitions of PRP.

Fifty-one COPD patients (FEV\textsubscript{1}: 57±17%L) underwent 10 weeks outpatient PRP supervised exercise training on a cycleergometer and upper limb training. Pre-PRP (T0), post-PRP (T1), 6 months (T2) and 9 months (T3) after the end of PRP we measured: exercise tolerance by 6 minute walking test (6MWT), dyspnoea by MRC, quality of life by St George Respiratory Questionnaire (SGRQ). All outcomes improved at T1. 6MWT and MRC progressively worsened at T2 and T3 respectively, whereas SGRQ remained stable up to 9 months from PRP.

P3646

Rehabilitation of pulmonary dysfunction in patients with ankylosing spondylitis

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Objective: The study is aiming to demonstrate the benefit of inspiratory muscle training (IMT) on pulmonary dysfunction in ankylosing spondylitis (AS) patients.

Methods: Twenty four patients (mean age: 45.6±6.5 years old, all males) who were previously diagnosed with AS stage III and IV were included in a eight week prospective study. The patients were evaluated at baseline and at the end of the study with respect to resting pulmonary function test (forced vital capacity - FVC, forced expiration volume in one second - FEV\textsubscript{1}) and cardiopulmonary exercise test (maximal minute ventilation - VEmax, maximal tidal volume - VTmax and maximal workload attained during the exercise test - PMax). All patients performed IMT sessions, three times weekly for a period of eight weeks using a computer assisted TrainAir device. Each IMT session was individualized by evaluating the maximum inspiratory pressure (SMIP), the training being performed at 80% of SMIP.

Results: Using paired t test to compare data at baseline and at the end of the study we noticed significant improvements of FVC (3.3%, p<0.0002), FEV\textsubscript{1} (3.2%, p<0.0047), VEmax (5.8 L/min, p<0.0002), VTmax (0.7 L, p<0.0248) and PMax (16 Watt, p<0.0001).

Conclusions: Inspiratory muscle training improves resting and effort pulmonary function of patients in advance stages of AS. This is mainly due to the influence of IMT on increasing strength and mobility of the diaphragm and accessory inspiratory muscles, together with the biofeedback provided by the interaction of patient - TrainAir system – physical therapist. Improving ventilometric performance leads to an increased exercise capacity and quality of life in patients with AS.

P3647

Complex outcomes of physical training in COPD patients

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Background: Exercise and respiratory training is an important part of COPD patient management. It improves physical tolerance and lung function, as well as HR QoL.

Aim: To assess the exercise and respiratory training impact on systemic effects in COPD patients.

Methods: 52 COPD patients, stage III and IV were randomized in 2 groups. Group 1 (63.9±7.5 yr, 34.6±11.5 pack/yr, FEV\textsubscript{1} 36.4±11.06% pred., FEV\textsubscript{1}/FVC 39.7±8.82%, CRP 10.7±6.84 mg/l, CD-ES 25.9±9.2) received ICs, LABA, long-acting bronchodilators. Group 2 (64.9±7.8 yr, 38.4±14.56 pack/yr, FEV\textsubscript{1} 33.8±16.4% pred., FEV\textsubscript{1}/FVC 41.3±10.8%, CRP 14.1±4.67 mg/l, CD-ES 26.8±8.5) - the same therapy - exercise and respiratory training: upper and low limb muscles training + Threshold IMT and PEP COPR IL I. IL6, TNF-a, testosterone, 6MWT, lung function, QoC MOS SF-36, CRC, CES-D depression questionnaire (17 points - not depressed, 18 and depression - ) before and after 4 weeks were evaluated.

Results: In group 2 there was the significant improvement in lung function (AFEV\textsubscript{1}: 11.1±8.7%, p<0.05), physical tolerance (6MWT: 85.3±5.77 m, p<0.01), inflammatory markers: ACRP: -8.3±1.67 mg/l, p<0.04, \Delta IL6: -3±4.4 pg/ml, p<0.05, \Delta IL1: -4.1±4.2 pg/ml, p<0.16, \Delta Testosterone: 0.79±0.62 mmol/l, p<0.001, QoC: 18.9±8.9, p<0.001, ADRP: 21.4±7.8%, p<0.05, \Delta MIH: 14.0±6.2%, p<0.001). CES-D was -9±4.6, 6 points. In the group 1 there was no significant improvement in all parameters. There was no significant changes in TNF-a in both group. Correlation: RV/TLc and CES-D r=0.70, FEV\textsubscript{1}/FVC and CES-D r=0.44, MH and CES-D r=0.72, SF and CES-D r=0.79.

Conclusion: Exercise and respiratory training has an effect on COPD patient systemic effects.

P3648

Prevalence of airflow obstruction according GOLD, ATS and ERS criteria in symptomatic ever-smokers referring to a pulmonary rehabilitation department

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Aim: To evaluate prevalence of airflow obstruction (AO) in ever-smokers ≥ 45 years old, all males.
years old with both dyspnoea and chronic productive cough, using European Respiratory Society (ERS) statement (FEV1/FVC < 80% predicted in men and women, respectively), American Thoracic Society (ATS) statement (FEV1/FVC < 75%), and Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement (FEV1/FVC < 70%).

Methods: Lung function tests were performed in all patients referred to our Pulmonary Rehabilitation department because of respiratory diagnosis or symptoms. For analysis, in patients showing AO we used post-bronchodilator lung function values.

Results: In 184 ever-smoker patients with symptoms of chronic obstructive pulmonary disease (COPD), the prevalence rates of AO were as follows: ERS = 89.7%, ATS = 76.6%, and GOLD = 63.6%. Patients with AO according ERS criteria showing severe to moderate (M2) obstruction (i.e. FEV1 < 70% predicted) were 373 months old. Patients with ERS MS AO but without AO using either ATS or GOLD criteria were 84.8% and 19.3%, respectively.

Conclusions: Prevalence of AO is highly dependent on which guidelines it is based. ATS and particularly GOLD statement can cause a large underdiagnosis even of moderate to severe COPD. Diagnosis of COPD may be overlooked if SVC is not performed.

P3649
Post-bronchodilator FVC determines pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease
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Chronic obstructive pulmonary disease (COPD) is an heterogeneous disease with various clinical and functional phenotypes, hence individualization of treatment strategies, such as pulmonary rehabilitation (PR), is important. Our aim was to explore the importance of post-bronchodilator forced vital capacity (pbFVC) in determining the effects of a PR programme on several patient-oriented outcomes.

In the absence of any comorbid restrictive disorder (such as pleural thickening, heated TBC, combined fibrosis, kyphoscoliosis, morbid obesity etc.), FVC reflects the mechanical constraint imposed by the elastic and resistive denouement of the lungs. We have studied 41 COPD patients (FEV1 39% ± 11% pred.) who completed a 3-month 36-session PR programme and who were evaluated before and after PR in chronic dyspnoea (modified MRC scale), exercise capacity [6-min walking distance (6MWD) and peak workrate on a maximal cardiopulmonary exercise testing (WRmax)] and health-related quality of life (SGRQ questionnaire). Patients were divided in two groups based on their pbFVC: Group A (FVC > 70% pred., n=20, patients, age 64.8±8 years) and Group B (FVC < 70% pred., n=21, patients, age 62.4±8 years). In patients of Group B we excluded on clinical & imaging grounds the presence of any comorbid disease with a potential to affect FVC.

Results: Post-bronchodilator FVC determines pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease (COPD).

P3650
Respiratory muscle strength and exercise tolerance before and after pulmonary rehabilitation in COPD patients
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Background: Patients with COPD have severe breathlessness induced by the increased mechanical work of respiratory muscles in relation to dynamic hyperinflation. Pulmonary rehabilitation programs have been shown to relieve dyspnoea, but the mechanism by which they succeed remains controversial.

Aim: To evaluate the effect of pulmonary rehabilitation on thoracic mechanics.

Method: The association between thoracic hyperventilation measured by plethysmography (functional residual capacity FRC, residual volume RV), respiratory muscle strength (maximal inspiratory pressure MIP, maximal expiratory pressure MEP) and dyspnoea scores (MRC, BORG scale) in patients with stable COPD before and after pulmonary rehabilitation (outpatient program, 2 months, 3 sessions/week, including daily respiratory muscle training).

Results: Twenty patients with COPD stage II-IV GOLD were included. Thoracic hyperventilation was present in all cases: mean FRC 164.9% of the predicted value and RV 209.2% before the rehabilitation program. Mean MIP was 69.6% and mean MEP 105.3%. The severity of dyspnoea before the pulmonary rehabilitation was negatively associated with inspiratory muscle strength (r =-0.68) and hyperventilation (r =-0.45). Hyperinflation decreased at the end of the rehabilitation program (mean RV decreased with 15.1% and mean FRC with 9.2%), mean MIP increased with 14.3% and the mean dyspnoea score decreased from 3.5 to 2.4.

Conclusion: Pulmonary rehabilitation optimized thoracic mechanics in our patients by reducing thoracic hyperinflation and increasing the effectiveness of inspiratory muscles work.

P3652
Asthma control (AC) 1 year after pulmonary rehabilitation (PR)
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Background: Only sparse data exist on the effectiveness of PR in asthma concern- ing AC. Therefore we conducted a prospective observational study to determine the effect of a 3 week inpatient-PR on AC.

Methods: From May to September 2009 all asthmatic patients of a pulmonary reha- bilitation clinic were asked to participate in the study. 201 out of 245 participated (83%). 42.3% were female, mean age 48.4 ± 9.5% patients from asthma GINA grade 3-4. Obligate components of PR were patient education, physical training, breathing retraining and psychosocial support. Primary outcome was AC (asthma control test, ACT), which was assessed at beginning of PR (T0), at discharge (T1), and 3 (T2), 6 (T3) and 12 months (T4) post PR. The three latter were delivered by mail. 83.5% (T2), 88.0% (T3) and 72.6% (T4) of the patients answered. Sec- ondary short-time outcomes were 6MWD and FeNO, which were measured at the beginning of PR (T0) and at discharge (T1).

Results: (mean ± st.dev., median): n=106, median ACE score: T0 16.0±5.2, T1 20.5±4.0*; T2 18.9±4.7*; T3 18.4±4.9*; T4 18.4±4.9*. FeNO: T0 76.0±38.8*; T1 23.3±18.8*; T2 5.1±3.2* (p-values <0.01 versus T0).

Discussion: The mean ACE score at baseline was 16.0 (of 25), indicating an uncontrolled asthma, while the mean score post PR was 20.5, e.g. indicating sufficient AC. Even after 1 year the mean ACE score of 18.4 indicates a significant improvement of AC. The proportion of patients with sufficient AC (ACT 20-25) increased from 33.2% to 67.4% after PR and was still 51% after 1 year.

Conclusion: PR lengthens the 6-MWD, reduces FeNO (significant improvement in both) and improves asthma control least for one year.

P3653
Quantification of smokers and smoking status among COPD patients, hospitalized for an exacerbation
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Background: In 2009, Dept of Pulmonary Medicine and Deps of Physiotherapy and Ergotheraphy, Gentofte Hospital, University of Copenhagen have carried out the pilot study “KOL-hjem-igen” (COPD-home-again) (COPD-2009). All patients included were transferred after an exacerbation of COPD 1.1.2009 to 31.12.2009 in COPD-home-again. This consists of open telephone line, home visits by a COPD nurse 5-7 days and 6 months after discharge, individual self-care plan, rehabilitation by physiotherapist and ergotherapist during admission including self-training plan and rehabilitation to visitation.

656s
Background and objective: Patients with chronic obstructive pulmonary disease (COPD) are commonly referred for pulmonary rehabilitation (PR), but there is limited evidence on the effect of home-based PR. The aim of this study was to determine the effect of a new home-based PR program toward expiratory airflow limitation among COPD patients.

Methods: 40 stable COPD patients (FEV1, 37.7 ± 13.0% predicted) were randomized to PR group (n=20) undergoing a 8 weeks home-based PR programme more suitable to respiratory physiology and control group (n=20). Baseline and post-PR variables were recorded, and changes in pulmonary function, respiratory muscle strength and quality of life (St. George’s Respiratory Questionnaire, SGRQ), as well as the body mass index, airway obstruction, dyspnea, and exercise capacity (BODE-index) were evaluated.

Results: After the PR programme, there were significant increases in respiratory muscle strength (P<0.001) and 6-min walk distance (422.9 ± 106.6 vs 473.3 ± 112.2 m; P<0.001) and significant reduction in SGRQ total score (49.4 ± 42.0 vs 36.9 ± 12.6; P<0.001). MRC dyspnea scale (2.9 ± 0.9 vs 2.0 ± 0.7; P<0.001) and BODE index (5.2 ± 2.1 vs 4.1 ± 1.7; P<0.001) in PR group but not in control group. However, no statistical significance was found in pulmonary function between the two groups (P>0.05).

Conclusion: We conclude that PR toward expiratory airflow limitation substantially improved respiratory muscle strength, exercise capacity, dyspnea, quality of life and the BODE index. Therefore, it could be considered as a new effective home-based PR method in stable COPD patients.

### P3654

**Impact of obesity on pulmonary rehabilitation in COPD patients**

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**Aim:** We aimed to examine the influence of pulmonary rehabilitation (PR) on pulmonary function test, body composition, exercise capacity, the perception of dyspnea, quality of life, muscle strength, anxiety and depression scores in obese and non-obese COPD patients.

**Methods:** We conducted a retrospective study of 82 patients with COPD who completed a 12-month PR program in our center. They were classified into two groups based on BMI: Underweight (BMI < 18.5 kg/m²) and overweight (BMI ≥ 30 kg/m²). The impact of PR on pulmonary function, body composition, exercise capacity, quality of life, muscle strength, anxiety, and depression scores were assessed.

**Results:** The BMI distribution was uniform among all patients with COPD. The results showed that PR had a significant impact on pulmonary function, body composition, and exercise capacity. The improvements were more pronounced in the non-obese group. The depression and anxiety scores were significantly reduced in the PR group compared to the control group.

**Conclusion:** Our results indicate that PR is an effective intervention for improving pulmonary function, body composition, and exercise capacity in COPD patients. The benefits of PR are more pronounced in non-obese patients.
P3659

Relationship between psychological well-being and lung health status in patients with bronchectasis

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Introduction: Patients with bronchectasis often experience depression and anxiety, but little information is available regarding patients with these conditions.

Aim of the study: This study was carried out to examine levels of anxiety and depression in patients with bronchectasis.

Methods: Fourty three patients with bronchectasis, determined by high resolution computed tomography scan, completed anxiety and depression questionnaires.

Results: 27% of patients had minor depression with an anxiety depression score more than 13 and 9% of patients had severe depression with an anxiety depression score more than 19. The anxiety depression status was not correlated to the extent of bronchectasis on CT scan (p=0.363). Post-brochodiathermy FEVI and higher airflow limitation were associated to a severe anxiety depression status.

Conclusion: Anxiety and depression are quite common in bronchectasis. Treatment in bronchectasis aimed essentially at reducing symptoms but it will not prevent levels of anxiety and depression which need alternative therapy.

398. Imaging in oncology and infectious diseases

P3660

Staging with FDG-PET/CT influences stage-specific survival in non small cell lung cancer (NSCLC)

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Background: Fluorodeoxyglucose (FDG)-PET/CT has a high sensitivity (89-100%) and reasonable specificity (79-95%) for the diagnosis of NSCLC. Currently it is mainly used in preoperative staging. In approximately 15% of these cases, it leads to the diagnosis of metastatic disease that was neither clinically suspected nor seen in conventional imaging. It may be assumed that integrating these cases in the palliative stage IV group, has an influence on overall survival.

Aim: To compare the overall survival (OS) of patients with stage IV NSCLC who underwent FDG-PET/CT staging with patients where conventional imaging procedures were performed.

Methods: We analyzed the OS of all patients diagnosed in 2009 (n=254), 96/254 (38%) patients were staged with PET/CT and 158/254 (62%) with conventional imaging (CT). Survival data were compared by Kaplan-Meier statistics.

Results: Patient in the PET/CT group (65±11) were younger than in the CT group (68±10 years; p = 0.008). The median OS of all patients was 246 (range: 217 – 275); 338 (range: 247 – 429) days in the PET/CT group and 207 (range: 161 – 253) in the CT group (p = 0.001).

Conclusion: FDG-PET/CT staging leads to earlier recognition of stage IV NSCLC patients and thus longer survival times. To what extend a selection bias for age and/or clinical condition may have influenced our results, needs to be discussed.

P3661

CT-guided transthoracic breast lesion location wire implantation for small nonpalpable pulmonary nodules

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Purpose: To evaluate the technique, safety and diagnostic reliability of transthoracic wire implantation for nonpalpable and invisible small pulmonary nodules (SPN) prior to video-assisted thoracoscopic surgery (VATS).

Methods: From April 2009 till January 2011, 17 patients underwent 18 VATS resections after insertion of a "breast lesion localization wire" (7.7 or 10.7 cm needle length and 20-gauche size) into a SPN. The wire was placed using a CT fluoroscopy procedure.

The patients were assessed with respect to localization and puncture of the lesion, duration and complication rate of the procedure, conversion thoracotomy rate during VATS and pathological results.

Results: Preoperative CT-guided wire implantation succeeded in all patients. The average CT-guided procedure time was 12 min (range 8-15 min) and no complication was noted. There was no conversion to thoracotomy needed in any patient. Histological assessment revealed metastases in 11 patients, non-small-cell lung cancer in 4 patients, interstitial fibrosis in 2 patients and a sarcoid nodule in 1 patient.

Conclusions: Percutaneous CT-fluoroscopy guided wire placement is a useful and safe technique for localizing nonpalpable pulmonary nodules during VATS resection.

P3662

Imaging techniques in the evaluation of solitary pulmonary nodules (SPNs)

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Despite new imaging techniques such as contrast enhanced computed tomography (CECT) or positron emission tomography with 18-fluorodeoxyglucose (FDG-PET/CT), non-invasive diagnosis of SPN etiology still remains a problem.

Aim: 1. to assess the incidence of malignancy in newly diagnosed SPNs 2. to evaluate utility of CECT and FDG-PET/CT in SPN diagnosis

Methods: 85 patients with newly diagnosed SPNs were observed on an ambulatory basis between 2008 and 2010. The diagnosis of malignant etiology of SPNs was based on pathological examination.

The benign etiology was proved based on either: 1. pathological examination 2. lack of growth for at least 2 years or resolution in radiological follow-up 3. central/total calcification in CT

The result of FDG PET/CT was suggestive for benign etiology of SPN if uptake of FDG was like background (SUV < 1) and the result of CECT if enhancement value was < 15HU.

Results: The SPN etiology was determined in 60 patients. 12 nodules (14%) were malignant, 48 nodules (56.5%) were benign. 17 patients are still under observation; 8 were lost to follow up. FDG-PET/CT was performed in 32 patients. In 16 cases the result was negative, 12 had an increased FDG uptake, 4 were inconclusive. The specificity, sensitivity, positive (PPV) and negative predictive value (NPV) and diagnostic accuracy of FDG-PET/CT were 91%, 87%, 83%, 93% and 88%, respectively. CECT was performed in 26 patients. In 10 cases the result was suggestive for benign SPN. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of CECT were 100%, 48%, 69%, 100%, and 58% respectively.

Conclusions: The diagnostic accuracy of FDG-PET/CT is higher than that of CECT. The advantage of CECT is its high sensitivity and NPV.

P3663

Prediction of the lung adenocarcinoma metastatic spread according to initial CT examination

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Adenocarcinoma of the lung gives a wide spectrum of different metastatic spread. Often we can find them before primary neoplasm. Therapy and prognosis depends not only on possibility of medicament or surgical treatment but also on location of neoplasm.

Aim of the study is to show spread direction of lung adenocarcinoma according to localization of primary neoplasm followed by computerized tomography.

Material and methods: This is study of 4356 patients with 14528 CT examinations.

All patients were with adenocarcinoma of the lung. All examination were performed on 16 or 64 MDCU. Using virtual bronchoscopy were it was possible. Metastatic spread was followed by conventional radiography, ultrasound, scintig-
raphy, MDCT and MRI according to location. Male patients were 2821 (64.76%),
female 1535 (35.24%). Middle age of patients was 68.3 years.

**Results:** We divided results according to lobar anatomy parts of the first sign
of neoplasms on initial CT examination, with hilar localization of neoplasms like
a separate entity. Neoplasms of both upper lung lobes were spread dominantly on
supra renal gland (67.14%), after that on liver and then on bones. Neoplasms of
middle right lobe was spread in both hilar regions. Basal tumors were mostly spread
in bones (34.73%) and after that in liver. Hilar neoplasm spread to brain mostly
(76.36%). Second group were patients we were find metastatic spread before
primary examination lung adenocarcinoma.

**Conclusion:** Spread prediction of lung neoplasm is very important for therapy
and prognosis. CT is golden standard for evaluation.

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**P3664**

**CT guided biopsy of thoracic lesions**

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**Purpose:** This study was designed to assess different variables of thoracic be-
nign and malignant masses on Computed tomography (CT) guided biopsy and
to identify the complication rate of procedure.

**Materials and methods:** We evaluated 757 CT-guided biopsies of thoracic lesions
performed from March 2004 to December 2008, retrospectively. All biopsies were
performed by one radiologist. The CTs were assessed by a trained general practi-
tioner for the size and location of lesions and pneumothorax or pneumomediastinum
diagnosis and then all CTs were double checked by the same radiologist. Lesions considered benign
or malignant based on pathology reports.

**Results:** Biopsy yielded sufficient tissue for pathologic examination in 612 cases
(80.8%); 224 lesions were benign and 388 lesions were 51.3% were malignant
(27 small cell and 233 non-small cell tumors). The most prevalent location of
lesions was Right Upper Lobe (182 cases). 78 masses were located in mediastinum
and 41 lesions in chest wall. 44.2% of benign lesions belonged to infectious
(69.7% bacterial, 20.2% fungal, 6.1% hydatid cyst and 4% TB) and the rest were
inflammatory masses (43.8%), granulomatous (5.8%) and neoplastic (6.2%) ones.
The mean size of benign and malignant lesions were 6.011 and 7.481 cm, respec-
tively (P<0.05). Complication presented in 40 cases; pneumothorax occurred
in 37 (4.9%) and bleeding in 3 (0.4%) patients.

**Conclusion:** CT-guided needle biopsy seems to be a reliable diagnostic modality
with low risk probability of complications for thoracic lesions.

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**P3665**

**An unusual opacity in lung lymphoma**

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Pulmonary localization of lymphoma is rare. It presents mainly in young patients
with various histological features

**Study objective:** To show an unusual cause of lung cavity

**Method:** In order to illustrate the atypical radiological presentations of lung lymphoma. We report a retrospective serie of four cases of lymphoma collected in our server for the size and location of lesions and pneumothorax, diagnosis and then all CTs were double checked by the same radiologist. Lesions considered benign or malignant based on pathology reports.

**Results:** Among the four cases of lymphoma, two were malignant and two were benign. All diagnoses were proven histologically by bronchial and nodal biopsies. Peripheral nodes were appeared very late after pulmonary localization

**Conclusion:** This study discusses difficult to differentiate between primary lung lymphoma and bronchial carcinoma; tuberculosis with Hodgkin’s disease and MALT lymphoma.

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**P3666**

**Lymphoma diagnosis on computed tomography guided needle aspiration and biopsy**

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National Institute of Tuberculosis and Lung Diseases, Tehran, Islamic Republic of Iran

**Background:** In recent years, CT-guided biopsy is going to be replaced with open
biopsy for Lymphoma diagnosis.

**Objective:** The aim of this study was to assess Lymphoma diagnosis on CT-guided
biopsy and to identify the complication rate of procedure.

**Methods:** We evaluated 78 CT-guided biopsies of mediastinal lesions performed
from March 2004 to December 2008, retrospectively. All biopsies were mostly spread
by one radiologist. The CTs were assessed by a trained general practitioner for the
size and location of lesions and pneumothorax or pneumomediastinum diagnosis
and then all CTs were double checked by the same radiologist. Lesions considered
benign or malignant and lymphoma based on pathology reports.

**Results:** Biopsy yielded sufficient tissue for pathologic examination in 63 cases
(80.7%); 14 lesions (17.9%) were benign and 49 lesions (62.8%) were malign-
ant. In malignant masses 15 Lymphoma (30.6%) and 20 other kinds of tumors
(46.8%) were found. Moreover, 1 Imalignant lesions had no differentiation. Among
Lymphoma lesions, there were 7 (46.7%) Hodgkin, 5 (33.3%) Non-Hodgkin Lymphoma
and 3 (20%) Lymphoma without differentiation. Pneumothorax or pneumomediastinum as complications did not present in any case.

**Conclusion:** CT-guided hilar biopsy seems to be reliable as a less invasive
diagnostic modality with low risk probability of complications for Lymphoma.

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**P3667**

**Regional ventilation distribution in experimental sub-lobar acute lung injury**

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**Introduction:** Electrical impedance tomography (EIT) is able to trace ventilation-
related changes in electrical properties of lung tissue. Previous studies using
computed tomography (CT) suggested a good correlation between regional EIT
data and lung tissue density. However, no validation data exist in regional acute
lung injury (ALI).

**Objective:** To validate EIT measurements of regional ventilation (rVa) by dynamic
non-multidetector-row CT (Xe-MDCT) in two animal models of regional ALI:
Methods: 9 anaesthetized mechanically ventilated pigs were examined before and
after induction of ALI within two adjacent sub-lobar lung segments by repetitive
saline lavage (n=4) or endotoxin sepsis injury (n=5). EIT data were acquired at 25 scans
(GeoEM B system, Carefil Fusion, Hochberg, Germany). Xe-MDCT (Sensation 64, Siemens AG, Forchheim, Germany) was performed at the same
thoracic region. EIT and Xe-MDCT rVa images during control and ALI were
divided into 32 regions of interest (ROI) in each hemithorax. rVa differences for
both methods were obtained by subtracting the corresponding values in each ROI.
EIT and CT measurements were compared by Spearman’s Rho correlation.

**Results:** In 4 of 9 animals analyzed so far, rVa difference images revealed a ventilation decrease in the injured (right) lung and an increase in the non-injured
(left) lung compared to control. rVa changes occurred in spatially similar locations.
Spearman’s rho ranged from 0.931-0.936 for the right and 0.943-0.979 for the left
hemithorax in control. All ALI groups were 0.857-0.933 and 0.948-0.981, respectively
(p<0.001).

**Conclusion:** A good correlation existed of rVa determined by EIT and Xe-MDCT
in the 4 animals with regional ALI compared to date.

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**P3668**

**CT findings in hantavirus pneumonia outbreak in children**

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Hantaviruses belong to the Bunyaviridae family of viruses. Like all members of
this family, Hantaviruses have genomes comprising three negative-sense,
stranded, linear RNA segments, so called class I RNA viruses. Viruses in the genus Hantavirus are unique in that they are transmitted by aerosolized rodent excreta or rodent bites, whereas all other genera in the
Bunyaviridae family are arthropod-borne viruses.

**Aim of the study:** The main aim is to show cases of Hantavirus pneumonia in
child population.

**Material and methods:** We examined 23 child patients with confirmed Hantavirus
pneumonia. The youngest patient was 4 years old, the oldest 16. We examined all
patients on 16 or 64 MDCT.

**Results:** After the major flood we had few outbreaks, one of them was Hantavirus
infection with mainly pulmonary form. All patients were from rural parts with no medical
institution near, so patients went to medical care in late phase of illness. In the first
phase symptoms were similar or same as influenza like fever, chills, sweaty palms,
diarrhea, malaise, headaches, nausea, abdominal and back pain, tachycardia and
hypoxemia but in the late phase occur a lot of different symptoms. CT signs develop
rapidly and constantly, first one sided mostly near hilum but as time goes by illness
going on other side. First radiology sign is similar to bronchiolitis and after that
massive inflammation, than again bronchiolitis in next lung segment. In the lethal
cases (8, 34.78%) illness develop for two months, each day symptoms were worse.
We had 3 patients with massive hemoptysis and bleeding after hemodialysis.

**Conclusion:** Lung form of Hantavirus illness is very often lethal. Understanding
the way of developing can be vital for patient life.

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**P3669**

**Radiological features of pneumocystis pneumonia (PCP) without HIV**

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**Purpose:** PCP occurs in immunosuppressed patients including those with malig-

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nancies. This study analyzed the relationship between the radiological features in chest X-ray and computed tomography (CT) of PCP patients without HIV and the outcome or patient’s background.

Methods: All 26 patients were diagnosed by respiratory samples combined with chest X-ray and CT findings. We retrospectively analyzed these data at the onset of the sickness.

Results: Twelve patients had malignancies. Fifteen patients had rheumatic and autoimmune disease. Steroid or immunosuppressive agents were administered in 72% and 40% respectively. Five patients received PCP prophylaxis. From a radiological point of view, chest X-ray revealed bilateral infiltration in 13 patients (52%). Chest CT showed a higher proportion of diffuse ground glass opacities (GGG) in 18 patients (72%). Consolidation and plural effusion were seen in 8 (32%) and 11 patients (44%) respectively and none had cystic lesions. All CT findings were classified as follows: 17 (68%) bilateral GGG either with sharp demarcation by interlobular septa (type A) or 4 (16%) without interlobular septal boundaries (type B). 2 (8%) infiltration mixed with GGG and consolidation (type C), 2 (8%) type D representing the rest cases. There was no correlation between these radiological features and outcomes.

Conclusions: Non-HIV PCP could show variety of radiological patterns and chest X-ray was not enough for the diagnosis of PCP. Despite our results, there still remains the possibility of the presence of the correlation of the radiological features or the patients background with the outcome and severity of PCP if more cases are studied. We expect more analysis to be done.

P3670
Primary versus acquired multidrug-resistant tuberculosis: Which are the true features of multidrug-resistant tuberculosis itself on thin-section CT
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Purpose: We designed this study to compare thin-section CT (TSC) findings of the primary multidrug-resistant (MDR) TB (MDR- P) and non-primary MDR TB (MDR-A) to those of drug-sensitive (DS) TB.

Materials and methods: We included 37 consecutive patients with MDR-P and 86 MDR-A who underwent TSC of chest. 123 patients with DS TB selected as a control group. Each DS TB patient was age and gender matched to a MDR TB patient. The frequency of lung lesion patterns in terms of tree-in-bud opacity/micronodules (TIB), nodule, consolidation, cavities, large fibrotic thin-walled cavity, and lobular volume decrease observed at TSC were compared among DS TB, MDR-P, and MDR-A.

Results: TIB (92%) and consolidations (76%) were most frequent findings of MDR-P. The frequencies of these are similar to those of DS TB (TIB for DS TB = 88%, p=0.561; consolidations = 81%, p=0.527). Cavities were next common finding of MDR-P (70%) and this frequency was similar to that of MDR-A (58%, p=0.260) than DS TB (38%, p=0.001). Volume decrease, large thin walled cavity, and pleural thickening were infrequent findings of MDR-P (22%, 5%, 1%, respectively) but common in MDR-A (56%, 30%, 42%, respectively), which mean chronic fibrotic condition.

Conclusion: Single or multiple cavities as well known typical feature of MDR TB are also common in MDR-P and not significantly different from MDR-A. In addition, MDR-P and DS TB reveal more common acute inflammatory findings (tree-in-bud pattern/micronodules, lobular consolidation, and overall consolidation) than MDR-A which reveal chronic fibrotic findings (thin walled cavity and volume decrease) in TSC.

P3671
Second year of H1N1 influenza: CT of the rare complications
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It is a second year of pandemic H1N1 influenza. Patients from second year of outbreak have a lot of differences than first year patients.

Aim of the study: The main aim is to show cases of influenza from the second year of outbreak and CT signs of rare complications.

Material and methods: We perform lung CT on 102 patients with positive H1N1 influenza. Patients were from 16 to 42 years old. Male were 58, female 54. All patients were examined on 16 or 64 MDCT using standard procedure and virtual bronchoscopy; we used also MDCT angiography in cases with high D-dimer test.

Results: This year outbreak has 3 different forms. First and most common form is abdominal with almost no lung symptoms. Second form has mostly neurological symptoms with few lung symptoms. Third form of outbreak has high lung symptoms with coughing, hypoxemia, pulmonary hypertension, high body temperature, nausea, vomiting, headache, neurological disorder, high blood pressure. In all 3 groups after first wave of illness second wave was with lot of different complications. In 17 patients we discover mediastinitis. In 3 patients we discover forms of bilateral pneumonolamomatosis, in 6 patients we find pulmonary thromboembolism, in 5 we find injuries of alveolar wall, in 2 patients we find massive hemoptysis, in 6 patients we find bilateral lymphadenopathy, in 1 patient we find dissecting aneurysm of aorta. We had 10 lethal cases. If we compare results with first year the percent of lethal cases is similar, also number of thromboembolism but everything else is different.

Conclusion: Second year of outbreak bring us different form of complications. MDCT have a significant place in detection of all lung complications.

P3672
Pulmonary hydatidosis mimicking metastatic malignancy
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Scattered pulmonary nodules are usually highly suspicious of metastatic malignancy, but can be one of radiological presentations of some infectious diseases such as hydatidosis. In order to analyse particularities of pulmonary hydatidosis mimicking metastatic malignancy, we report 5 cases of patients hospitalized in the pulmonary department of the Tunis Chest Disease and Surgery Training Hospital. The average age was between 36 and 74 years. The clinical features were dominated by haemoptysis (4 cases) and cough (2 cases). Chest radiograph showed disseminated pulmonary opacities in all cases. CT scan of the chest was helpful for diagnosis. Fibreoptic endoscopy performed in all cases showed hydatid membrane and confirmed the diagnosis in 2 patients. Investigation ELISA for Echinococcus was positive in all cases. Four patients had pulmonary embolic hydatidosis due to the involvement of right cardiac cavities. One patient had bronchogenic hydatidosis due to the rupture of pulmonary cysts into bronchi. Medical treatment (albendazole) was performed in all patients associated with surgical treatment in 2 cases. After treatment, 2 cases of recurrence were noted.

Figure 1. Disseminated pulmonary hydatidosis.

P3673
Disseminated pulmonary hydatidosis. Disseminated pulmonary hydatidosis may present diagnosis difficulties particularly with metastatic malignancy. Its management is difficult and costly.

P3674
Does it matter who requests HRCT scans?
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Introduction: High resolution computerised tomography scanning (HRCT) is 660s
widely used for the investigation of interstitial lung disease (ILD) and bronchiectasis. If significant numbers of inappropriate scans were requested it could be argued that its use should be restricted to senior chest physicians only.

Methods: All HRCT scans performed over an eight month period between January - August 2009 at our hospital were identified and only those that had been performed as an initial investigation into suspected ILD/bronchiectasis were included. The x-ray card and clinic letters were analyzed to see who had requested them.

Results: 82 HRCT scans were eligible for inclusion. 30/43 (69.8%) of the scans requested by respiratory physicians confirmed the suspected diagnosis compared with 24/39 (61.5%) by non-respiratory physicians (p = 0.4892). 12/17 (70.6%) of the scans requested by respiratory trainees confirmed the diagnosis compared with 42/65 (64.6%) requested by consultant physicians (p = 0.7774).

Conclusion: There was no significant difference in the number of negative scans requested by non-respiratory and respiratory physicians or between respiratory trainees and Consultants. We therefore suggest that the use of HRCT scanning should not be restricted to senior respiratory specialists.

P3675 Lung tularemia in patients with tuberculosis presented by CT
Aleksandar Ivkovic1, Tamara Milosavljevic2, Zoran Radovanovic1. 1Center of Radiology, Clinical Center Nis, Nis, Serbia; 2Radiology, ZC Vranje, Vranje, Serbia

After the major flood we had outbreak of tularemia. Tularemia, also known as rabbit fever, is a disease caused by the bacterium Francisella tularensis. Depending on the site of infection, tularemia has six characteristic clinical syndromes: ulceroglandular, glanderous, oropharyngeal, pneumonic, oculoglandular, and typhoidal. Outbreak becomes more frequent with high rate of tuberculosis.

Aims: The main aim is to show cases of tularemia on patients with tuberculosis.

Methods: We examined 63 patients with acute form of lung tularemia who already had tuberculosis (from 186 patients with lung tularemia). Male patients were 48, female were 15. Patients were from 48 to 87 years old. We examined all patients had tuberculosis (from 186 patients with lung tularemia). Male patients were 48, female were 15. Patients were from 48 to 87 years old. We examined all patients on 16 or 64 MDCT.

Results: After the huge flow in several rural parts, there were outbreaks of tularemia. 186 patients were with syndromes of lung pneumonia with symptoms of fever, chills, headache, muscle aches, joint pain, dry cough, and progressive weakness. Patients also develop chest pain, difficulty breathing, bloody sputum, and respiratory failure. In 63 we find signs of all forms of tuberculosis. Developing of symptoms occurs faster in those patients with bizzare radiology signs from military form to caverns filled with acute areas of tularemia grow. CT findings of the lungs were developing in few steps with progression even when other symptoms were gone. First we find enlargement of the hilar region of the lungs and after few day illness develop into the lung parenchyma, firstly retro hilum and after that slowly on the whole lung, part by part with bronchiolitis.

Conclusion: CT has a significant role in determining and following all of form of lung diseases.

P3676 Interpretation of chest radiographs from children with lower respiratory tract infections
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Introduction: Pneumonia is a common diagnosis amongst children admitted to hospital. Diagnosis relies upon accurate chest radiograph interpretation. This study compared levels of agreement amongst paediatric clinicians and consultant paediatric radiologists when interpreting CXRs.

Methods: Four paediatric radiologists, independently interpreted 5 radiological features (and no features) for each of 30 CXRs, randomly selected from 100 radiographs attained over two years from children with fever & signs of respiratory distress aged 6 months to 16 years. The same CXRs were then interpreted by 21 other paediatricians with varying experience level. Agreement split by grade and specialty, was analysed using free-marginal multirater Kappa, assuming no prior expectation of the proportion of radiographs with each feature.

Results: Agreement (~1 relates to complete disagreement, 0 to chance agreement, and 1 to complete agreement)

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<td>0.96</td>
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Conclusion: Paediatric radiologists showed high levels of agreement for all features. Normal CXRs and pleural effusions were identified consistently amongst all 25 clinicians. However, interpretation of all other features had lower levels of agreement within non paediatric radiologists. This highlights the need for more rigid training in interpreting CXRs for paediatricians and the early reporting of CXRs by paediatric radiologists.

P3677 Usefulness of vibration response imaging (VRI) for pneumonia patients
Kwang Ha Yoo, Kye Young Lee, Sun Jong Kim, Won Dong Kim, Hee Jong Kim, Eugene Park. Department of Pulmonology, Internal Medicine, Konkuk University Hospital, Seoul, Korea

Background: Pneumonia is commonly seen in outpatient clinics, and it is the most common cause of death in infectious disease. Pneumonia is diagnosed by symptoms, chest X-ray and blood tests. chest X-ray and blood tests have its limitations and primary care clims usually do not have adequate diagnostic tools. VRI is a new diagnostic modality and the procedure is non-invasive, radiation-free, and easy to handling. The aim of this study was to evaluate the diagnostic usefulness of the VRI test in pneumonia patients and the correlation between other conventional test such as Chest X-ray, Laboratory tests and clinical symptoms.

Methods: VRI was performed in 57 patients who diagnosed with pneumonia in Konkuk University Medical Center. VRI was measured in a quiet room initially and after treatment. The change of Chest X-rays, CRP, WBC, Body temperature were compared with the change of VRI during time course.

Results: Mean age was 60 years, and average follow up periods was 7.1days. VRI, chest X-ray and CRP was significantly improved after treatment. Correlation with VRI and other test was not seen all patients. But female patients and relatively severe pneumonia patients showed correlation with VRI and chest X-ray.

Conclusion: This study demonstrates that VRI can be safely applied to patients with pneumonia.

P3678 Fungus ball diagnosed on computed tomography (CT) guided needle biopsy of thoracic lesions
Mehrdad Bakhshayesh, Pooeyeh Grahil, Soheyla ZahiriFarid. Radiology Department, National Research Institute of Tuberculosis and Lung Diseases, Tehran, Islamic Republic of Iran

Background: CT-guided biopsy provides results in a short period and can be applied on outpatient and even high risk patients however; some studies do not recommend it in lesions with benign histology probability.

Objectives: To report our experience regarding fungus ball diagnosis on CT-guided biopsy and to identify the complication rate of procedure.

Materials and methods: We evaluated 99 CT-guided biopsies of infected thoracic lesions performed from March 2004 to December 2008, retrospectively. All biopsies were performed by one radiologist by westcott needle number 20 and 18. The CTs were assessed by a trained general practitioner for the size and location of lesions and pneumothorax or pneumomediastinum diagnosis and then all CTs were double checked by the same radiologist. Lesions considered fungus and their differentiations based on pathology reports.

Results: During four year study 20 fungus lesions (15 male and 5 female) were found with the mean age 54.75 years (ranging: 19-77). In these series there were 16 (80%) Aspergillosis, 2 (10%) Mucor mycosis and 2 undifferentiated fungus ball. The mean diameter of lesions and lesion distance to chest wall was 5.650 cm (range: 1 to 11.5) and 0.75 cm (range: 0 to 3), respectively. Nine (45%) fungus lesions were located in left upper, 4 (20%) in right lower, 4 (20%) in right upper and the rest (15%) in left lower and right middle lobes. Pneumothorax occurred in 2 cases (1 Aspergillosis and 1 Mucor mycosis) while chest tube was placed only in 2 cases (1 Aspergillosis and 1 Mucor mycosis) while chest tube was placed only for patient with Mucor mycosis to manage the complication.

TUESDAY, SEPTEMBER 27TH 2011
Methods: Patients with different indications for endobronchial biopsy underwent three hot and three cold endobronchial biopsies with a random fashion. All biopsies were obtained with a single biopsy forceps with and without the application of an electrocoagulation current, set on soft coagulation mode (120W). A four point scale was used for quantification of bleeding. A single pathologist blinded to the patients’ history was requested to review all samples. A three point scale was used to assess electrocoagulation damage.

Results: A total of 240 biopsies were obtained from 40 patients. Frequency of positive concordance between the two methods was 85%. The degree of electrocoagulation damage of the samples was as follows: grade 1=52.5%, grade 2=32.5%, and grade 3=15%. The average bleeding score following hot biopsy was significantly lower compared to the cold biopsy (p=0.006). The concordance between diagnostic yield of hot and cold biopsies was 85%. There was no significant difference between the diagnostic yields of two biopsy methods (p=0.687).

Conclusions: In this study, hot biopsy forces significantly decreased the procedure related bleeding and minimally impaired the quality of samples. Regarding low prevalence of bleeding following endobronchial biopsy, routine use of hot bronchoscopy forceps is not reasonable. However, familiarity of bronchoscopists with this method may improve bronchoscopy safety.

P3680
Evaluation of lung biopsy techniques for diagnosis of idiopathic interstitial pneumonias
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Aim: To assess and compare efficacy and safety of medical thorascopic lung biopsy with transbronchial lung biopsy (TBLB) for diagnosis of idiopathic interstitial pneumonias.

Material and methods: 59 patients with restriction on spirometry (Mean FVC -1.14 litres), exertional dyspnoea and interstitial pattern on HRCT (non classical for UIP) underwent lung biopsy using medical thoracoscopic forceps. 31 patients with comparable clinical profiles subjected to bronchoscopy and TBLB were used as controls.

Results: (Study group) Overall diagnostic yield was 98.3%. UIP (59.3%) was most frequent histopathological pattern. There were no intraoperative or immediate post-operative complications. Eventual complications included (in 19 patients) air leaks and prolonged ICD drainage (10), Delayed wound healing (3) and need for ventilatory support (5). Average duration of ICD was 4.81 days and average length of hospital stay was 6 days. There were 5 deaths within 1 month of the procedure (1 attributed to ischemic heart disease and Left ventricular failure, two to nosocomial pneumonia, two to unknown cause post discharge). Prolonged prior steroid use was single important factor associated with increased incidence of complications (14/23 complications in patients steroids vs. 5/16 complications in patients off steroids) (p<0.05).

In the control group conclusive diagnosis was reached in 3/31 cases (1Sarcoidosis, 1 DIP, 1 BOOP). Total score was before RT =3.1, just after RT = 5, at 3 months follow up = 4, at 6 months follow up = 3. Significant difference was observed between before and after RT (p=0.047) and between 3 months and 6 months (p=0.011).

Conclusions: 1. Medical thorascopocnic Lung biopsy has higher diagnostic yield than TBLB. (98.1% vs 97.3%) (p<0.001). 2. Prolonged prior steroid use is associated with increased incidence of complications (p<0.05).

P3681
Serial transbronchial biopsies in patients with lung cancer after radiation therapy
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Background: Radiation therapy (RT) may cause lung damage in patients with lung cancer. However, serial microscopic evaluation of human lung parenchyma after irradiation is lacking. Transbronchial biopsy (TBB) is a bronchoscopic sampling tool for a variety of bronchial and pulmonary lesions.

The aim of the present prospective study was to assess lung parenchyma lesions after RT by serial TBBs.

Methods: 14 patients with lung cancer necessitating radiation therapy agreed to participate the study. Of these patients, 12 (85.7%) were assessable. TBB were obtained to the opposite of the tumor. Serial TBBs were performed before, just after RT and every 6 months in the first year of follow-up. Evaluation of each specimen was based on the presence of congestion, inflammation, hemorrhage and fibrosis, all these parameters giving a final total score.

Results: A median number of 4 biopsies were taken per patient and per procedure (range 2-6). In 11/12 patients (91%) congestion was present within the period of follow-up. All these patients presented a late evolution of a different degree of fibrosis at their TBB. Total score was before RT = 3±1.3; just after RT = 5±1.3 and at 6 months = 6±1.9. Significant difference was observed before between and after RT (p=0.047) and before and at 6 months after RT (p=0.011). Major limitation of the study was the low patient accrual due to the proposed repeated procedures in patients with advanced stage disease and, at the end, poor performance status (overall median survival after RT 8 months).

Conclusions: An increase in the number of biopsies in irradiated patients may be associated with an increased incidence of complications. A total score of >6 suggests a significant degree of inflammation and fibrosis. Other parameters of radiation pneumonitis may also contribute to the final total score.
The combined conventional bronchoscopic methods are still useful in diagnosis of sarcoidosis

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Introduction: At present EBUS-TBNA and EUS-FNA methods are suggested as the best methods in diagnosis of sarcoidosis. Until now a lot of pulmonologists use the standard endoscopic procedures to confirm this disease. In our study we present the results of the combined conventional bronchoscopic methods such as endobronchial biopsy (EBB), transbronchial lung biopsy (TBLB), transbronchial needle aspiration (TBNA) in diagnosis of patients with suspicion of sarcoidosis.

Material and methods: 53 patients with suspicion of sarcoidosis (in stage 1 to 3) were sent to Division of Bronchoscopy for all 2009 year. The all patients were underwent bronchoscopy with simultaneous all three bronchoscopic methods. The presence of noncaseating epithelioid cell granulomas that correspond to clinical and radiological picture of sarcoidosis was observed in 94.33%. In only one patient the sarcoidosis was confirmed by EBUS-TBNA, and two others with acute sarcoidosis still remain under clinical observation.

Conclusions: The results of combined bronchoscopic biopsies are comparable to the results from EBUS and EUS studies. It might suggest that the combined conventional bronchoscopic methods are still useful and recommended to confirm sarcoidosis suspicion.

Safety and efficacy of outpatient bronchoscopy in lung transplant recipients: A single centre retrospective analysis

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Bronchoscopy is an important diagnostic and therapeutic tool for the management of patients after lung transplantation. Out-patient bronchoscopy attempts to improve quality of life of transplant recipients and reduce health costs through reducing hospitalization. Limited data exists however, regarding safety and efficacy of outpatient bronchoscopy.

Between August 2008 and January 2011, we analysed outpatient bronchoscopies in our program. Post-bronchoscopy a routine monitoring for at least one hour, excepted patients with transbronchial biopsies, was performed. 3.197 outpatient bronchoscopies were performed in 571 lung transplant recipients. Analysis indicated a median bronchoscopic rate of 4 examinations per patient (interquartile range 10-20 minutes) was identified, 14% had intravenous sedation and 4% antitussive medication. Interventions performed included bronchial alveolar lavage (BAL) in 81%, transbronchial biopsy (TBB) in 23%, balloon dilatation in 4% and argon ablation.

Conclusions: Efficacy of TBLB plus BAL in sarcoidosis diagnostics was 102/127 (80.3%). Among the rest 38 cases with non-effective biopsy, diagnostic changes in BAL were found in 13 cases, total efficacy was 95/127 (75%). Among the rest 38 cases with non-effective biopsy, diagnostic changes in BAL were found in 13 cases, total efficacy was 95/127 (75%).

French national survey by the GELF on flexible bronchoscopy, patients, indications, results and complications

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Objective: Estimate the indications and the results of the flexible bronchoscopy in France in 2009.

Materials and Methods: The GELF led a forward-looking investigation in Mars 2009 with 150 pulmonologists distributed in a random way on the territory by a questionnaire of 2 patient cases. An extrapolation of procedures was realized over the year and on the number of worked days.

Results: A number estimated by 352 500 flexible bronchoscopies were realized in 2009. 64% of the procedures were made in public hospital and 36% in a private clinic. More of ¼ acts were made ambulatory or conventional hospitalization. In 74% of the cases, it was about an initial diagnosis. 2/3 of the patients had never had previous bronchoscopy. Average age: 62,5 years, 24% were women and 67% of smoking (39 PA). 48% were referred by the general practitioner. 72% of procedures were realized under local anesthetic. The main indications were the thoracic lesion (47%), the other one were, surveillance of bronchial cancer, low respiratory infection, hémoptysie, diffuse infiltrative lung disease, chronic cough, pleural effusion and suspicion of tuberculosis. The bronchoscopy was pathological in 59% of the cases. For more half, the histology revealed a bronchial cancer, mainly squamous cell (35%). The main complications were the bronchosopame (8%) and the bleeding (5%).

Conclusion: This survey of the GELF is the first study allowing the extrapolation of the number of annual bronchoscopies in France, the results and complications. The bronchoscopy allows on the national level, the diagnosis of a significant number of bronchial cancers.

ENDOBRONCHIAL ULTRASOUND USING A GUIDE SHEATH FOR PERIPHERAL PULMONARY Lesions: Experience From the First Year

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Background: Transbronchial biopsy (TBB) for peripheral pulmonary lesions (PPLs) is usually performed with help of fluoroscopy, but the yield varies widely. This feasibility study aimed to assess ability of endobronchial ultrasound guide sheath (EBUS-GS) to provide imaging guidance for TBB.

Methods: Twenty-eight patients with PPLs were prospectively enrolled and underwent bronchoscopy with fluoroscopy and EBUS-GS procedure. In this procedure, the probe covered by a GS was introduced into the lesions via the working channel of bronchoscope. The probe was withdrawn, while the GS was left in situ. A brush or biopsy forceps were introduced through the GS into the lesions.

Results: Mean size of PPLs was 2.4±1.0 cm. Twelve of 28 patients (42.9%) was diagnosis by the EBUS-GS procedure. Also, the diagnosis was 30.8% (4/13) for benign disease and 80% (8/10) for malignant PPLs (p = 0.036). There was no statistically significant difference between diagnostic yield and size of the lesions, positive CT bronchus sign, and the EBUS probe located either within lesions or adjacent to lesions. Fortunately, no major complication was observed.

Conclusions: EBUS-GS is a safe and useful method for collecting samples from malignant peripheral pulmonary lesions.

EFFICACY OF TRANSBRONCHIAL BIOPSIES WITHOUT FLUOROSCOPY CONTROL IN DIAGNOSTICS SARCIOIDOSIS

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Background: Currently diagnosis of sarcoidosis, most common entity among interstitial lung diseases, should be confirmed by biopsy during bronchoscopy, with routine BAL. Unfortunately, sometimes there is no fluoroscopy control in bronchoscopy room, thus the yield of the obtained biopsies is considerably lower.

Aim: To evaluate the efficacy and safety of “blind” transbronchial biopsy (TBLB) with BAL during flexible bronchoscopy (FB).

Materials: 127 patients with newly diagnosed sarcoidosis undergo the FBS with TBLB and BAL. Frequency of pneumothorax/severe bleeding, median number of tissue samples, presence of lung tissue in sample, evidence of granuloma in histology and cytology, diagnostic changes in BAL were analyzed.

Results: There were 71 female in the group, mean age was 39.5 yrs, varied from 16 to 69. Mean duration of disease since first symptoms/chest abnormalities detection was 47.8 weeks. There were no cases of pneumothorax or severe bleeding after procedure. Mean tissue samples number was 3.1, varied from 1 to 6, median 2.

Lung tissue was observed in 118/127 cases (93%). Granuloma was found in 82 out of 118 patients (64.6%), in cytology additionally granuloma was found in 7 patients, so the total efficacy was 89/127 (70%). Among the rest 38 cases with non-effective biopsy, diagnostic changes in BAL were found in 13 cases, total efficacy of TBLB plus BAL in sarcoidosis diagnostics was 102/127 (80.3%).

CONCLUSION: Bronchoscopy with TBLB and BAL even without fluoroscopy control is effective and safe method of diagnostics in newly diagnosed sarcoidosis.
and its defining criteria were suggested as factors impacting the diagnostic value of TLBB. This study aimed at evaluating the factors affecting TLBB results in order to increase the diagnostic value of this method. This was a prospective, double-blind observational analysis. We had a total of 44 patients with pulmonary lesions; each of these patients underwent 4 biopsies. Biopsy samples were taken using cup and alligator forceps alternatively. From 88 samples obtained by the alligator forceps, 16 were diagnostic while from the same number of specimens taken by the cup forceps, 21 samples had diagnostic value. Of the small sized samples (57 cases), 12 (21.1%) were diagnostic while among the 66 medium sized samples, 12 (18.2%) and from the 53 large sized samples, 13 (24.5%) were diagnostic. Among samples floating on the surface of the liquid (48 cases), 6 (12.5%) had diagnostic value. Of the 12 samples suspended in the liquid, 2 (16.6%) and among the 116 samples precipitated to the bottom, 29 (25%) were diagnostic. Of the 84 samples with more than 20 alveoli, 31 (36.9%) were diagnostic. Among 26 samples with number of alveoli less than 20, 5 cases (19.2%) were diagnostic. This correlation was statistically significant. In a conclusion, number of alveoli present in the tissue sample was directly correlated with its diagnostic value. However, this study did not find a significant correlation between the diagnostic value of TLBB and type of forceps, sample size and flotation of the sample in the liquid.

P3690
Diagnostic value of the bronchoscopy in the focal pulmonary malignant lesions
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Introduction: A focal pulmonary lesion (FPL) is defined as an intraparenchymatous pulmonary lesion that is well circumscribed and completely surrounded by healthy lung.
Objective: To analyze the diagnostic value of the fiberoptic bronchoscopy (FB) in the malignant FPL in the last 18 months, concurrently with a change in the medical staff.
Material and methods: Cross-sectional study of all the FBs done at our Unit between 02/2008 and 08/2009 in patients with a solitary FPL with a definitive diagnosis of malignancy. The diagnostic value by size and site was analyzed with Pearson’s chi² statistics.
Results: We studied 131 patients of whom 107 (82%) were men. The area around the site is showed in the table (in 7 cases, the size was not determined).

<table>
<thead>
<tr>
<th>Size of FPL</th>
<th>Diagnostic Value</th>
<th>Size of FPL</th>
<th>Diagnostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 cm</td>
<td>100 (92%)</td>
<td>1–2 cm</td>
<td>74 (78%)</td>
</tr>
<tr>
<td>&lt; 1 cm</td>
<td>0 (0%)</td>
<td></td>
<td>67 (70%)</td>
</tr>
</tbody>
</table>

Possible to be determined (23 central and 1 peripheral). The media size of the FPL was 2.1 cm. The diagnostic value of the FB was 0.73 and of the TBB with 0.67. The combination of AFB and AFS is effective in determination of malignancy (P = 0.03). This correlation was statistically significant. In a conclusion, number of alveoli present in the tissue sample was directly correlated with its diagnostic value. However, this study did not find a significant correlation between the diagnostic value of TLBB and type of forceps, sample size and flotation of the sample in the liquid.

P3692
Combined endoscopic evaluation of the effectiveness of neoadjuvant chemotherapy of NSCLC using autofluorescence and spectroscopic methods
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Objectives: To estimate the informativity of autofluorescence bronchoscopy and spectroscopy for evaluating the effectiveness of neoadjuvant chemotherapy (NCT) for lung cancer.
Material and methods: The study included 46 patients with central NSCLC IIIa/T1b stage who underwent 2-4 courses of platinum-based NCT. Endoscopy was done before treatment started and repeated each 21 day. Combined endoscopic investigation included: bronchoscopy in conventional mode (CB), spectroscopy in conventional mode (CS), bronchoscopy in autofluorescence mode (AFB) and spectroscopy in autofluorescence mode (AFS). Integrated system for autofluorescence and spectroscopy ClearVu Elite (Perceptronix Med. Inc., Canada) was used. The data obtained were compared with the results of histological study of biopsy samples from the respective sites.
Results: The sensitivity and specificity of the combination of AFB and AFS was 97.1% and 88.3%, respectively vs. CB and CS - 66.7% and 86.9%, respectively. Combined endoscopy revealed that the NCT was effective in 41.3% cases (n = 19 - partial endoscopic response), in 4 patients (10.3%) endoscopic tumor progression was found. Endobronchial spread of the tumor in 30.4% of cases (P = 0.03) was defined more accurately by AFB and AFS in comparison with CB and CS, it was important for choosing a volume of further resection. In 97.1% of cases, the data AFB and AFS is fully consistent with the results of histological studies (P = 0.02).
Conclusions: The combination of AFB and AFS is effective in determining margins of central lung cancer spread and effectiveness of NCT.

P3693
Changes of the pulmonary arteries in patient with pulmonary hypertension: Using optical coherence tomography
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Objective: To assess clinical using of optical coherence tomography (OCT) in patient with pulmonary artery hypertension (PAH).
Design and method: We studied the condition of vessels in a patient with systemic sclerosis and PAH. Our patient was a woman of 57 years. In the study, we used the following equipment specifications: IVUS (Eagle Eye Gold, catheter 40 MHz; In., USA), OCT (Light Lab Imaging Inc.) and general characteristics of different tissues by OCT.
Results: Cardiac catheterization showed pulmonary artery pressure of 90/20/35 mm Hg. Pulmonary capillary wedge pressure - 9 mm Hg. Both IVUS and OCT visualized the anterior basal segment pulmonary artery at the level of 16.3 mm (coronary area) by IVUS and at the level of 16.7 mm by OCT. Intima thickness was 0.41 mm by IVUS and 0.68 by OCT. We analyzed the tissue characteristics of the segment by OCT. We didn't find the scar borders, irregular borders or superficial signal. Thus we didn't find any features of calcium, lipids or mural thrombosis. The predominant tissue of the defected segment was homogenous bright tissue, e.t. fibrosis. We attempted to use radiofrequency analysis (VIH by IVUS), but, because of its lower resolution in the case of pulmonary arteries, in comparison to the coronary arteries, it turned poor information.
Conclusions: In the case of PAH IVUS looks like a method, which underestimates the intima thickness, in comparison with OCT. OCT enables to detect morphological features and possible injuries of the inner layer of the vessel wall. However, like any new technology, OCT will require a learning curve, to improve our ability and optimize treatment of patients with PAH.

P3694
Acriflavine-aided confocal laser-endomicroscopy for evaluation of central airway lesions
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Endobronchial ultrasound (EBUS) is a useful diagnostic tool to localize peripheral pulmonary lesions. Histopathological examination of these lesions is important for selecting patients eligible for surgical resection. A definitive diagnosis is often not possible, however, due to technical limitations of standard biopsy procedures. We report a patient with pulmonary artery hypertension (PAH). In the case of PAH IVUS looks like a method, which underestimates the intima thickness, in comparison with OCT. OCT enables to detect morphological features and possible injuries of the inner layer of the vessel wall. However, like any new technology, OCT will require a learning curve, to improve our ability and optimize treatment of patients with PAH.

Conclusion: The diagnostic value of the FB was 0.73 and of the TBB with radiographic guide was 0.53, being a difference by size but not by site.

P3691
Endobronchial ultrasound in the diagnosis of peripheral pulmonary lesions
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Endobronchial ultrasound (EBUS) is a useful diagnostic tool to localize peripheral pulmonary lesions (PPLs) and to guide transbronchial biopsy (TBB). We retrospectively evaluated the diagnostic accuracy of EBUS-guided TBB in comparison with a definitive diagnosis established by transbronchial CT-guided needle aspiration or surgical lobectomy. In the last ten months, 168 patients performed bronchoscopy for a PPL (mean diameter = 3.5±2.1 cm). PPL was visualized in 123 patients (73%) and TBB was performed in 117 patients. These patients had a PPL larger than patients with a non visualized lesion (mean diameter 3.7±2.1 vs 2.3±1.6 cm, respectively). A definitive diagnosis was obtained in 77 patients whereas 40 patients were lost to follow-up. The TBB diagnosis was cancer in 45 patients and non-malignant lesion in 32 patients. The definitive diagnosis was cancer in 67 patients and non-malignant lesion in 10 patients: all these 10 patients without cancer were correctly diagnosed with TBB.

In conclusion, the sensitivity of EBUS-guided TBB in the diagnosis of cancer was 67% (45/67) and the overall diagnostic accuracy was 71% (45+10/77). Our data confirm that EBUS-guided TBB is a sensitive method with a high diagnostic yield in patients with PPLs.
Combined endoscopic evaluation of central lung cancer spread using autofluorescence and spectroscopy

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Objective: To estimate the diagnostic value of autofluorescence bronchoscopy with spectroscopy in determination of lung cancer endobronchial spread.

Material and methods: The study included 78 patients with central NSCLC stage II-IV. Combined endoscopic investigation included: bronchoscopy in conventional mode (CB), spectroscopy in conventional mode (CS), bronchoscopy in autofluorescence mode (AFB) and spectroscopy in autofluorescence mode (AFS). Integrated system for autofluorescence and spectroscopy was used. The data obtained were compared with the results of histological study of biopsy samples from the respective sites.

Results: The sensitivity and specificity of the combination of AFB and AFS was 97.1% and 88.3%, respectively vs. CB and CS - 66.7% and 86.9%, respectively. Maximal diagnostic value had green-red ratio (GRR) • ratio of intensity in the green range (500-565 nm) to the red range (620-760 nm). For normal tissue mean GRR was 3.4±0.9, on the borders of tumor growth in 97% of the cases did not exceed 2.0 (mean 1.2±0.4) (p = 0.02), over areas of tumor tissue – in all cases less than 1.0 with an average of 0.7±0.2 (p = 0.001). In 97.1% of cases, the data AFB and AFS is fully consistent with the results of histological studies (p = 0.02).

Conclusions: Combination of AFB and AFS helps to objectively and accurately establish the boundaries of the tumor spread in bronchus/trachea.

Afibronectin and August band imaging videobronchoscopy in detection of premalignant bronchial lesions

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Background: The search for most efficient bronchoscopic imaging tool in detection of early lung cancer is still active. The major aim of this study was to determine sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of each technique and their combination in detection of premalignant bronchial lesions.

Patients and methods: Ninety six patients were enrolled in the study. Major indications were: radiological suspicion for lung cancer, surveillance of patients after surgery, evaluation of known malignancy, positive sputum cytology and prolonged cough. Lesions were classified as visually positive if pathological fluorescence was observed under AFB or, dotted, tortuous and abrupt ending blood vessels were identified under NBI. Squamous metaplasia, mild, moderate or severe dysplasia and CIS were regarded as histologically positive lesion.

Results: Sensitivity, specificity, PPV and NPV of WLBI in detection of premalignant lesions were 26.5%, 63.9%, 34.4% and 55.4% respectively, corresponding values for AFI were 52%, 79.6%, 64.6% and 95.9% respectively, for NBI were 66%, 84.6%, 75.4%, 77.7%, respectively, while corresponding values for combination of NBI and AFI were 86%, 86.6%, 84.6%, and 88% respectively. Combination of NBI and AFI significantly improves sensitivity when compared to each individual technique (p<0.001). When specificity is of concern combination of techniques improves specificity of WLBI (p<0.001), specificity of AFI (p=0.03) but it has no significant influence on specificity of NBI (p=0.53).

Conclusion: Combination of NBI and AFI in detection of premalignant bronchial lesions increases both sensitivity and specificity of each technique.
Expansion Factors 2.76 Tant, 4.0 Omni & 4.9 Hypaque. Tantulum results in CT metallic artifacts, but appears distinct under fluoro. Omni-Hypaque have softer outline simulates “typical” nodules, but progressively leaches radioopacity over 4-6 hrs. Complications include traumatic pneumothoraces.

Conclusions: Transbronchoscopic delivery of Radioopaque Hydrogels effectively simulate tumors usable for development of bronchoscopy enhancement software, and as targets for animal lab practice.

400. A little bit of everything: interventional pneumology

P3700
Role of medical thoracoscopy in a developing country: A single unit experience from Sri Lanka

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Introduction: Medical thoracoscopy (MT) is proven as an effective tool in managing pleural disease, but is scarcely available in resource poor environments.

Objective: To describe the utility and safety of MT in managing exudative pleural effusions in the local setting.

Method: We retrospectively analyzed 96 MTs performed during past year in our unit.

Results: 8 MTs failed due to non-collapsible lung (6) and poor patient compliance (2). Of the 88 where visualisation of pleural cavity was possible, 51 had septate deposits (19), oesophageal rupture (2) and chylothorax (1) in the cohort. During postoperative hospital stay ranged between 2 to 21 days (mean: 3.4 days). The results were very good in 654 patients (88%), acceptable in 71 patients (9.6%), and there was a failure in 18 patients (2.4%) after 4 months follow-up.

Conclusions: Thoracoscopic talc pleurodesis is a safe, economical and effective treatment for malignant pleural effusion.

P3702
Classification of findings during medical thoracoscopy: Do they correlate with pathology?

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Medical thoracoscopy although not always conclusive, has been established as the last step in the diagnostic approach of pleural effusion. We aimed to assess its diagnostic value and classify endoscopic findings in correlation with histology diagnosis.

During the last 5 years, 69 patients (55 males) aged 66±14 (mean±st.dev) underwent medical thoracoscopy in our unit for an undiagnosed exudative pleural effusion following extensive workup. Pleural biopsy revealed malignant pleural mesotheloma (MPM) of various subtypes in 16 (23.2%), non small cell lung cancer (NSCLC) in 9 (13%), extrathoracic malignancy in 3, paramalignant effusion in 2, angiosarcoma in 2 and Non-Hodgkin lymphoma in 1 patient. In 33 cases (47.8%) biopsy revealed chronic inflammation or "non specific pleurisy".

Endoscopic findings were classified as: pleural thickening, bulging, nodules, adhesions, diffuse infiltration, pleural masses, plaques, hemorrhagic appearance, visceral pleura invasion, pulmonary atelectasis. No significant correlations were found between endoscopic and pathology findings. However, parietal pleural mass had a trend of positive correlation with NSCLC (kappa=0.415, p=0.001) and a trend of inverse correlation with non specific pleurisy (kappa 0.35, p=0.001).

Medical thoracoscopy enabled specific diagnoses in more than 59% of prior undiagnosed cases in which all other means had been exhausted. High incidence of MPM in our patients is worth noting. The rest (47.8%) of the cases with non specific findings are continuously under follow up for a possible relapse or change in diagnosis. Endoscopic findings cannot predict final histology which remains the cornerstone of diagnosis.

P3703
Use of indwelling pleural catheters for management of recurrent chylothoraces: secondarily to benign superior vena cava syndrome: A case report

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We describe a unique case of intravascular (Hickman(c)) catheter-induced chylothoraces. They were treated with conservative measures and bilateral indwelling pleural catheters (PleurX(c)) insertion. The uniqueness of this case is that chylothorax re-appeared after re-institution of the patient diet, despite removal of the Port-
P3704

Impact of a new bedside thoracic ultrasound service in a large district general hospital: A service evaluation

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Background: In 2008, the UK National Patient Safety Agency (NPSA) issued an alert recommending the use of thoracic ultrasound to aid chest drain insertion (NPSA/2008/RR0003). Our institution is a large district general hospital in North-West England, serving a local population of approximately 330,000 people and a further 12 million holidaymakers who visit the area each year. In 2009, a Physician-Led Ultrasound Service (PL-US) was launched, in addition to the existing Radiology-Led Ultrasound Service (RL-US).

Aim: To investigate the demand for PL-US and the impact on workload and training.

Methods: We audited the number of procedures performed by physicians and radiologists from May-July 2008, 2009 and 2010.

Results: The total number of procedures increased from 24 (all RL-US) in 2008 to 66 (29 RL-US and 32 PL-US) in 2009. The proportion of RL-US procedures requested by respiratory medicine fell from 46% (11/24) in 2008 to 17% (4/24) in 2009 and 14% (4/29) in 2010, with the remaining RL-US procedures requested by other specialties. In addition, in 2010 a total of 24 thoracic ultrasounds were performed on respiratory patients, 20 of these 24 were performed by the PL-US, with the remaining 4 by the RL-US.

Conclusions: Overall demand for thoracic ultrasound has risen by 275% since the UK NPSA alert in 2008. Since introduction of the PL-US, the total number of chest medicine referrals to the RL-US has fallen by 64%. In addition, 83% of radiologists from each specialty who have used the service felt the training imparted to them was beneficial. Importantly, training opportunities for radiologists have not diminished as a result of this service.

P3705

Impact of teaching and awareness programme on doctors’ knowledge of chest drain insertion site

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Aim: To assess if doctors identify correct site for chest drain insertion. To assess impact of teaching programme on their knowledge.

Methods: In 2008, 111 doctors were asked to identify correct drain insertion site for uncomplicated pneumothorax by marking photographs. Data were collected on grade, specialty and prior experience (Gallagher JL; Stevenson N. Thorax 2009; 64(Suppl IV):A166). In 2010, 102 doctors surveyed after introduction of teaching programme.

Results: We had 108 responses in ’08 compared to 100 in ’10. 55/108 (51%) correctly marked site in 2008 compared to 75/100 (75%) in 2010.

Table 1: O2 therapy by mask

<table>
<thead>
<tr>
<th>Grade</th>
<th>2008, No. (%)</th>
<th>2010, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation Doctor year 1 (F1)</td>
<td>14/27 (52)</td>
<td>8/28 (29)</td>
</tr>
<tr>
<td>Foundation Doctor year 2 (F2)</td>
<td>8/11 (73)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Senior House Officer (SHO)</td>
<td>12/27 (45)</td>
<td>6/19 (32)</td>
</tr>
<tr>
<td>Specialist Registrar (SpR)</td>
<td>13/29 (45)</td>
<td>2/21 (10)</td>
</tr>
<tr>
<td>Associate Specialist</td>
<td>N/A</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>Consultant</td>
<td>6/14 (43)</td>
<td>6/22 (27)</td>
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</table>

Table 2: O2 therapy by TTO

<table>
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<tr>
<th>Grade</th>
<th>2008, No. (%)</th>
<th>2010, No. (%)</th>
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<tbody>
<tr>
<td>Foundation Doctor year 1 (F1)</td>
<td>14/27 (52)</td>
<td>8/28 (29)</td>
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<tr>
<td>Foundation Doctor year 2 (F2)</td>
<td>8/11 (73)</td>
<td>26 (33)</td>
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<tr>
<td>Senior House Officer (SHO)</td>
<td>12/27 (45)</td>
<td>6/19 (32)</td>
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<tr>
<td>Specialist Registrar (SpR)</td>
<td>13/29 (45)</td>
<td>2/21 (10)</td>
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<td>Associate Specialist</td>
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<td>1/4 (25)</td>
</tr>
<tr>
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<td>6/22 (27)</td>
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Table 3: O2 therapy by mask

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<tr>
<td>Foundation Doctor year 1 (F1)</td>
<td>14/27 (52)</td>
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<tr>
<td>Consultant</td>
<td>6/14 (43)</td>
<td>6/22 (27)</td>
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</tbody>
</table>

Conclusions: Overall demand for thoracic ultrasound has risen by 275% since the UK NPSA alert in 2008. Since introduction of the PL-US, the total number of procedures increased from 24 (all RL-US) in 2008 to 66 (29 RL-US and 32 PL-US) in 2009. The proportion of RL-US procedures requested by respiratory medicine fell from 46% (11/24) in 2008 to 17% (4/24) in 2009 and 14% (4/29) in 2010, with the remaining RL-US procedures requested by other specialties. In addition, in 2010 a total of 24 thoracic ultrasounds were performed on respiratory patients, 20 of these 24 were performed by the PL-US, with the remaining 4 by the RL-US.

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**P3708**

Two cases of benign tracheal stenosis successfully treated by minimally invasive endobronchial intervention


**Case no. 1:** In Oct. 2008 a 71 y.o.lady underwent thyroidectomy. After the operation bilateral vocal cord paralysis appeared causing dyspnea. A tracheostomy tube was placed to ease breathing. In two weeks time vocal cord function came back, however attempt to remove tracheostomy tube was unsuccessful because of symptoms of tracheal obstruction. We met the patient in June 2009. FBS disclosed a mass of granulation tissue obstructing trachea. Microbiologic examination of bronchial aspirate showed MRSA infection. By using rigid bronchoscopy granulation tissue was removed and 15-mm straight silicone stent was placed in the narrowed segment of trachea and antibacterial treatment was prescribed. A couple of days later the stent migrated, so it had to be repositioned and sutured to the anterior wall of trachea by transcutaneous transtracheal suture. The stent was removed two months later. There are no signs of tracheal stenosis observed during the following 2 years.

**Case no. 2:** A 76 y.o. lady was operated on in Febr. 2009 for perforative colitis. Postoperatively she had tracheostomy placed with ventilatory support for a week. Soon after discharge from hospital the lady noticed cough and progressive dyspnea. She was admitted to our hospital in Sept.2009. On FBS we found granulation tissue mass obstructing trachea. There was Ps. aeruginosa grown in the bronchial aspirate. Granulations were removed by using rigid bronchoscope and endobronchial argon plasma coagulation and the patient received antipseudomonal antibiotics. The procedure had to be repeated in 3 weeks time. Afterwards our patient recovered well and there has not been recurrence of tracheal stenosis observed.

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**P3709**

Comparison of I-gel and laryngeal mask for fibrobronchoscopy

Svilen Alexov, Dimitar Kostadinov, Danal Petrov, Anesthesia and Intensive Care Clinic, University Pulmonary Hospital, Sofia, Bulgaria; Bronchoscopy Department, University Pulmonary Hospital, Sofia, Bulgaria; Thoracic Surgery Clinic, University Pulmonary Hospital, Sofia, Bulgaria.

**Background:** The I-gel is a novel supraglottic airway device. Because of it’s design, material and small noninflatable cuff we hypothesized that it might be at least as effective as routinely used laryngeal mask (LM) in facilitating fibrobronchoscopy and artificial ventilation, but with less throat complaints.

**Objective:** To evaluate the efficacy of I-gel for providing adequate ventilation, good conditions for fibrobronchoscopy and patient’s safety under intravenous anesthesia in comparison with classically used LM.

**Methods and patients:** Two randomized groups were formed: I-gel (226pts) and ML (21pts). Anesthesia was induced and maintained with Propofol, Succinylcholine +/- Atracurium. Devices were positioned (size 4 for women and 5 for men) and IPPV with 100% O2 was started. We measured: time to successful insertion, success rate of insertion on first attempt, airway peak and leak pressure, We monitored the changes of tidal volumes (VT), airway peak pressures (PAW), end-tidal CO2, gas leakages (% of VT) when bronchoscope was at bronchial level. Postoperatively patients were interviewed for throat complaints, bronchoscopists for fibroscopic glotic view.

**Results:** The success rates of insertion were 21/22 (95%) for I-gel and 19/22 (90%). I-gel group showed significantly shorter mean time to insertion (12.2±6.9 vs 18.6±8.9 p<0.05), better fiberoptic view 3/22 (14%) vs 7/21 (33%) p<0.05 less postoperative complaints like soar throat, numb tongue, dysphagia, dysphonia, lip and dental trauma. 4/22 (18%) vs 8/21 (38%) p<0.05. Other postoperative data revealed no significant differences: VT, leak pressure, lost of VT and others.

Conclusions: I-gel facilitates fibrobronchoscopy and patient’s safety to greater extent than classical LM.

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**P3710**

Feasibility and safety of propofol sedation in flexible bronchoscopy

Peter Greendkleimeier, Gabriel Kurer, Eric Pflihm, Michael Tammi, Daiana Stolz. Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital Basel, Basel, Switzerland

**Background:** Propofol is a sedative-hypnotic with a rapid onset of action. There are only limited data evaluating propofol for flexible bronchoscopy. We analyzed the feasibility and safety of propofol for bronchoscopy in a high output tertiary care center.

**Methods:** Prospective data on patients undergoing flexible bronchoscopy at the University Hospital Basel were included. Patient demographics, ASA class, Mallampati class, indication for bronchoscopy, bronchoscopic procedures, duration of examination, medication requirements, minor and major adverse events, hemodynamic parameters, as well as cough scores during the procedure were documented. Patients were followed up to discharge from the bronchoscopy suite.

**Results:** Data on 440 patients with mean age 60 years (± 15.5, 200 male) were analyzed. Most common diagnostic procedures were bronchoalveolar lavage in 253 cases (31.5%) and bronchial washing in 174 cases (21.7%). The mean duration of the procedure was 19.6 min (± 12.08). The mean propofol dose was 200 mg (± 107.5) corresponding to 1.9 mg/kg (± 1.70). Minor adverse events included transient desaturation in 72 (16.4%), hypotension in 68 (15.4%) and minor bleeding in 11 (2.5%) patients. No major adverse events were recorded. The median decline in systolic blood pressure after initiation of sedation was 14 mmHg (± 28). A drop in systolic blood pressure greater than 20 mmHg was observed in 166 of the 440 patients (37%).

**Conclusion:** Propofol sedation for flexible bronchoscopy is feasible and safe.

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**P3711**

Predicting sedation in flexible bronchoscopy

Ruth Mc Donagh, Sheikh Shabbaz, John O’Neill, Eddie Moloney, Stephen Lane. Respiratory Medicine, Adelaide and Meath Hospital, Incorporating the National Children’s Hospital, Dublin, Ireland.

**Introduction:** Since 1985, midazolam has been widely used along with fentanyl for sedation in bronchoscopy. The aim of this study was to establish a correlation between patient age and the amount of midazolam required to produce adequate sedation.

**Methods:** Medical records of all the patients who underwent bronchoscopy in 2010 were accessed. Adequate sedation was defined as “a drug-induced depression of consciousness during which patients respond purposefully to verbal commands”.

**Results:** Of all patients (n=511), 54.4% were male and 45.6% female. Median age and dose of midazolam (range) was 60 years (16-91) and 6mg (0.14) respectively. The Spearman Rank correlation between sedatives and age were: midazolam (r= -0.486, p<0.000) and fentanyl (r= -0.396, p<0.000). Analysis of variance showed that every decade of increase in age saw a decrease in the dose of sedation required, and the difference in means of the dosage in each age group was statistically significant (p=0.000).

**Conclusions:** There is a statistically significant correlation between age and amount of sedative required. We can predict the dose of sedation required in flexible bronchoscopy in different age groups. Dose of one sedative agent can be used to predict the dose of the second.

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**P3712**

A retrospective audit of lidocaine use at bronchoscopy in a UK district general hospital

Claire Lawless, Salim Meghjee. Respiratory Medicine, Pinderfields General Hospital, Wakefield, West Yorkshire, United Kingdom.

**Introduction and aims:** Bronchoscopy is a commonly used investigation and Lidocaine is widely used as a local anaesthetic agent. Toxic side-effects of Lidocaine include cardiac collapse and seizures. The recommended dose in cardiac/hepatic insufficiency is 5mg/kg and 8mg/kg in all other patients. It is postulated that some patients may be given above the recommended dose.

**Methods:** 26 patients were identified retrospectively over a 3 month period. The patients were identified on the hospital bronchoscopy database. Case-notes were also analysed.

**Results:** Patient Mean age was 62.25years (30-86). 12 males (46.15%). Patient weight 71.54kg (42.65-117). 5 patients had cardiovascular disease. 4 patients had hepatic disease. 7 (77%) of these 9 patients received a dose of Lidocaine over the maximum for their weight. None of the patients without cardiac/hepatic disease received over the maximum dose of Lidocaine. All patients who were given over their maximum calculated Lidocaine dose or who were given within 100mg of...
their maximum dose were reviewed with particular reference to their weight. The Mean weight in this subset was 60.6kg.

Discussion: Patients in this group were frequently given more than their calculated maximum dose of Lidocaine at bronchoscopy. Those most at risk had cardiac or hepatic insufficiency. Patients who were given too much Lidocaine or who were within 100mg of being given too much had a lower Mean weight than that of the whole of the group by 10.8mg.

Conclusions: Lidocaine use is necessary for patient comfort and success of bronchoscopy. However, it seems more commonplace than previously thought to give higher doses of Lidocaine than those recommended.

P3713
Patient comfort score at bronchoscopy
Alina Ionescu, Katie Pink. Respiratory Medicine, Royal Gwent Hospital, Newport, Wales, United Kingdom

The aim of this study was to assess the patient comfort score immediately after bronchoscopy (by nursing staff and patient) and later on at follow up (by patient) in a teaching hospital.

Subjects and methods: One hundred and four consecutive patients (62 male, mean (SD) age 63.2 (15.6)) were included and complete data was analysed for 96. The index for bronchoscopy was radiological suspicion of lung cancer (39), haemoptysis (25), slowly resolving pneumonia (18), radiological picture of interstitial lung disease (16), cough (4) and mediastinal lymphadenopathy (2).

The nurses used a patient comfort score (1-mild to 4-severe) and a sedation score (1-awake, 2-sedated). While in recovery and then again at follow up appointment (7-14 days later) the patients were asked to describe their comfort score (1-mild to 4-severe). Patients received Midazolam for sedation (1-7 mg i.v.) and local anaesthetic Lignocaine 2%.

Data was analysed in Spss and correlation coefficients; Chi square Kruskal Wallis used.

Results: The comfort score by nurses correlated with the score by patient in recovery (p=0.006) and at follow up (p=0.03). The two patient scores correlated (p=0.001, Pearson’s r=0.5). No difference in the comfort scores was found when the grade of the operator, dose of Midazolam, type of local anaesthetic, specimens taken, patient’s position or the recovery sedation score were taken into account.

To conclude, the patient comfort score assessed by nursing staff is a good indicator of the patient’s own perception of their discomfort at bronchoscopy. The patient perceived comfort score is not different after the sedation effect of Midazolam has worn off compared to the score assessed immediately after the bronchoscopy.

P3714
Patient satisfaction survey on bronchoscopy explanation
Rajesh Kumar Yadavilli, Ian Webster. Thoracic Medicine, Royal Bolton Hospital, Bolton, Lancashire, United Kingdom

Background: Bronchoscopy is routinely performed by the chest physicians and is data presented in the patients before they give written consent. We wanted to see if anxious patients need higher doses of sedation.

Methods: Patients were asked to fill the satisfaction questionnaire with 8 domains just before undertaking procedure. Interpreters were used for the non-English speaking patients.

Results: 61 patients, undergoing bronchoscopy between Jan 2009 to Jun 2009 answered survey questions with domains in (Table 1) rating their satisfaction between 1-10. Ratings >6 were considered good response except for domain 8 where <5 considered less anxious.

Table 1

<table>
<thead>
<tr>
<th>S. No</th>
<th>Patient satisfaction domains</th>
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<th>%</th>
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<tbody>
<tr>
<td>1</td>
<td>Understand the exact reason for test</td>
<td>39 / 61</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Understand procedure</td>
<td>50 / 61</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Understand complications</td>
<td>49 / 61</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Understand post procedure care</td>
<td>54 / 61</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Involvement of patient to have the test</td>
<td>56 / 61</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Satisfaction on written information</td>
<td>48 / 61</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>Satisfaction on time and venue</td>
<td>59 / 61</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Anxiety about the test</td>
<td>27 / 61</td>
<td>44</td>
</tr>
</tbody>
</table>

22% did not receive written leaflets. Of 27 anxious patients, only 7 (26%) needed more sedation than the mean dose of 2 mg midazolam and 6/34 (18%) less anxious patients also had bigger doses.

Conclusions: Patients were generally satisfied with our bronchoscopy explanation. There is poor correlation between anxiety ratings and doses of sedation. Educating trainees on broncoscopy explanation, repeating verbal information about procedure with patients at the time of consent and just before the test and giving written leaflets to all the patients at first explanation should improve overall satisfaction.

P3715
Fiberoptic bronchoscopy assisted percutaneous dilatational tracheostomy: How safe is for an intensivist to perform it?
Kyriaki Ftzikouktsis, Georgios Korotkamion, Christos Tsakalakis, Panagiotis Zotos, Nikodimos Katsarelis, Paraskevi Spyrou, Konstantinos Tsiromas, Michalis Pedemonos. ICU, General Hospital of Athens 'G. Germenis1', Athens, Greece

Background: Intensive care unit (ICU) patients, mainly those who need prolonged ventilator support, may require tracheostomy, which once was done in the operating room. Percutaneous dilatational tracheostomy was first described in 1985 and is now a well-established procedure that can be performed at the bedside by an intensivist with less surgical equipment required.

Aim: To evaluate the safety of performing percutaneous dilatational tracheostomy (PDT) with Fiberoptic bronchoscopy assistance in patients requiring prolonged mechanical ventilation.

Material and method: Sixty three patients 17-85yrs of age, 28 females and 35 males underwent PDT due to prolonged endotracheal intubation between December 2009 and January 2011. The procedures of percutaneous dilatation tracheostomy with guide wire dilator forceps (GWDF) were done bedside with bronchoscopic guidance under general anaesthesia in the ICU department. Operative and post operative complications were observed.

Results: Overall complication rate was low and occurred in 5 patients (7, 9%). There was no procedure-related mortality. Subcutaneous emphysema without pneumothorax occurred in one patient, one patient had a transitory hypotension related to sedation and three patients had peristomal oozing. The mean time for completion of the procedure was 15 minutes and no patient required conversion to surgical tracheostomy. The bronchoscopic examination that was performed in 38 of the patient 20 days after tracheostomy tube removal showed no scar formation.

Conclusion: PDT with bronchoscopic guidance is a safe and easy procedure that can be done by an intensivist at the bedside setting.

P3716
Outcomes and complications of bronchoscopy-guided percutaneous dilatational tracheostomy
Jose Andres Garcia Romero de Tejada1, Rosa Mar Gomez Punter 1, Ian Carrasco Barber2, Ricardo Andino Ruiz2, Javier Aspa Marco2, Olga Rajas Naranjo1, Servicio de Neumología, Hospital Universitario de la Princesa, Madrid, Spain, 1 Unidad de Cuidados Intensivos, Hospital Universitario de la Princesa, Madrid, Spain

Background: Percutaneous tracheostomy (PT) is one of the most frequently performed procedures in Intensive Care Unit (ICU). As many as 10% of patients requiring at least 3 days of mechanical ventilation will receive a tracheostomy. Some of the complications can be severe and can be prevented with bronchoscopic assistance.

Aim: To investigate the outcome and complications of bronchoscopy-guided PT.

Material and methods: 59 patients was prospectively included from March-November/2010. Demographic data, time of procedure and complications were monitored. Patient’s heart rate, blood pressure and continuous pulse oximetry were monitored. All PT were performed under bronchoscopic control at the patient’s bedside in the ICU by an medical intensivist and a pulmonologist. Statistical software Sigma-Stat 3.5 was used.

Results: 54% of patients: male. Patient mean age: 60. Mean body mass index: 25.2 (Standar Error Mean-SEM 0.5). Mean APACHE index: 20.1. SAPS: 44.5. The reason for admission at ICU was due to medical conditions (70%) and surgical/polytraumatism (30%). Indication for PT: coma (47%), intubation weaning failure (34%), neuromuscular failure (9.4%) and prolonged endotracheal intubation (9.4%). Mean duration of PT: 3.5 min. Main complications: O2 desaturation <90% (7.7%), submucosal tunnlealization of tracheal wall (3.8%), tracheal ring break (1.5%), bleeding requiring hemostasis (5.7%) and major hemorrhage requiring blood transfusion (2%). Extubation, early decannulation, injury to posterior tracheal wall, and barotrauma were not described.

Conclusions: PT is a safe technique. The use of bronchoscopy reduces duration of procedure, decreases morbidity and can identify complications missed by a “blind” approach.

P3717
The real-interventional-bleeding simulator: A new training and education model for interventional bronchoscopy
Martin Hackl1, Armin Saltzmann1, Michael Loeis2, Klaus Lenke2, Herbert Jannig1. 1Pneumologie, Thalk LH, Natter, Natters, Tirol, Austria; 2Arachtis, Prodesis, Heiligkreuzsteinach, Heidelberg, Germany

Introduction: Biosimulation models might play a crucial role to train interventional procedures especially acute endobronchial bleedings. The simulation of an repeated emergency situation enables the bronchoscopist and his team to act professionally.

Background: Until now the available models couldn’t reproduce this key aspect in interventional bronchoscopy in a satisfactory way.

Methods: We developed a new biosimulation model with 2 transparent covers and a free moving diaphragm. The control unit with an vacuum pump allows full...
Conclusion: This model might be helpful to develop algorithms for all interventional procedures especially connected to the handling of bleedings.

P3718
Improved diagnostic of electromagnetic navigation bronchoscopy in peripheral lung lesions: Are the size and the bronchus sign important?
Olga Rajas Naranjo, Rosa Mar Gómez Punter, Jose Andrés Gª Romero de Tejada, Emma Vazquez Espinosa, Julio Añócoche Bermúdez, Javier Aspa Marco.
Servicio de Neumología, Hospital de la Princesa, Madrid, Spain.

Background: Electromagnetic navigation (EN) is a technique that can be used with bronchoscopy to obtain samples of small peripheral nodular lesions. It enables both transbronchial biopsies and fine-needle aspiration to be performed. EN can obviate the need for more invasive diagnostic procedures thus saving time and avoiding complications.

Aim: To evaluate the diagnostic yield of electromagnetic navigation-guided bronchoscopy (ENB) in patients with peripheral lung lesions and analyze the results according to the size of the lesion and the presence of a bronchus sign in the computed tomography (CT).

Patients and methods: From April 2009–October 2010, 50 consecutive patients were included. We used the Bronchus® system (Superdimension) with a therapeutic bronchoscope (Olympus, working channel 2.8mm). All subjects had CT scans of the chest, configured with slices of 1-2 mm thickness at 1-1.5 mm intervals in DICOM format.

Results: 70%: male. Median age: 69. The average size of the lesions was 22.6 mm (≤20mm: 19 (38%) and >20mm: 31 (62%)]. Mean duration of the intervention: 25 mm. Diagnostic rate of this procedure was 67%; 61% for lesions ≤20 mm in diameter; and 71% if >20mm. The bronchus sign (BS) was identified in 44% of cases. In patients with BS, the diagnosis yield increased until 82% and when BS was negative: 54% (statistically significant variable).

Conclusions: FBEN is a safe method that increases the diagnostic yield of peripheral lung lesions. 67% of cases resulted in obtaining diagnostic tissue. If BS was identified, diagnostic yield was statistically significant increased. There was no relation with lesion’s size.

P3719
Transbronchoscopic 3D volumetric optical coherence tomography (OCT) imaging of airways
Jiefeng Xi1, Xingde Li2, MingYing Zeng3, Sheng Xu4, Rex Yung5, 1Whitaker Biomedical Engineering Institute, Dept of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States; 2Whitaker Biomedical Engineering Institute, Dept of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States; 3Medicine, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States; 4Department of Nuclear Medicine, St Antonius Hospital, Nieuwegein, Netherlands; 5Whitaker Biomedical Engineering Institute, Johns Hopkins University School of Medicine, Baltimore, MD, United States.

Introduction: OCT, a non-invasive optical modality capable of high-resolution cross-sectional imaging of tissue microanatomy, holds potential of "in-vivo" diagnostics of pathology. Development of miniature probes & laser sources have advanced real-time OCT imaging of small structure such as airway morphologies.

Aim: To develop 3D volumetric OCT imaging of airways.

Method: IRB approved porcine protocol. Airways imaged with a 1300-nm swept-source OCT at a 40 kHz A-scan rate, placed within a 1.3 mm catheter advanced through 2 mm bronchoscope channel. Axial & lateral resolution of the system is ≤2 μm and ~20 μm in tissue, respectively. 3D volumetric imaging achieved by rotating the OCT catheter while pulling it back (similar to spiral CT), at an imaging speed of 10 frames/sec & helical rotation pitch of ~100 μm.

Results: 3rd to 7th generation airways imaged, spiral scanning data recorded, then processed. In addition to presentation as isolated axial slices, playback can present spiral imaging reformatted as 3D volumes plus virtual fly-through of airways.

Conclusion/clinical significance: Transbronchoscopic OCT imaging can generate high-res axial imaging of airway microstructures. Reconstruction of dataset generates dynamic 3D imaging. In-vivo temporal monitoring of pathologic events such as cancer progression or physiologic effects of bronchoconstriction in airway disease will advance diagnosis and management of lung diseases.
with chronic sarcoidosis remain unclear. We wanted to assess clinical benefit and safety of long-term infliximab treatment in patients with chronic steroid-resistant sarcoidosis.

Methods: A retrospective chart review of all patients with chronic steroid-resistant sarcoidosis who received infliximab between January 2003 and November 2010. Pulmonary function tests and index lesions before and after infliximab therapy were assessed.

Results: 28 patients received infliximab, 16 of them for more than 12 months. 5 (31%) of these 16 patients with long-term infliximab treatment had a predominately pulmonary and 11 (69%) a predominantly extrapulmonary disease. Mean duration of treatment was 29 months (range 12 - 62). 6/11 (55%) patients with mainly extrapulmonary sarcoidosis showed a complete remission of their index lesion, 4/11 (36%) had a partial remission, and 1/11 (9%) showed no response. 1/5 patient with predominantly pulmonary sarcoidosis showed a >10%-improvement of percentage predicted forced vital capacity (FVC/P%); 3/5 showed a 0.10%-improvement, and in 1 patient FVC/P% declined. Thus, overall 14/16 (88%) patients profited from long-term infliximab treatment. Suspected adverse effects which lead to a temporarily discontinuation of infliximab therapy were noticed in 1/16 (6%) patient.

Conclusions: This retrospective study indicates that long-term infliximab is very efficient and safe in patients with chronic steroid-resistant sarcoidosis when assessed with individualized treatment targets. Patients with predominantly extrapulmonary sarcoidosis seem to profit more than patients with predominantly pulmonary disease.

P3724 Interferon gamma release assays in screening for tuberculosis – Can we use them in patients with sarcoidosis?

Nils Milman1, Claus B. Svendsen1, Bolette Sobo1, Aase B. Andersen2
1Department of Rheumatology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 2Department of Respiratory Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Treatment with tumour necrosis alpha (TNF-α) inhibitors has been introduced in recalcitrant sarcoidosis. These biologics may reactivate a latent tuberculosis infection (LTBI) and sarcoidosis patients are routinely LTBI tested before receiving TNF-α inhibitors. Until now, the tuberculin skin test (TST) has been used for LTBI screening among sarcoidosis patients in Denmark, even though the TST is unreliable with a low sensitivity in this specific group of patients. This study reports the results of an LTBI screening among sarcoidosis patients in Denmark. Background: Cardiac sarcoidosis (CS) is an inflammatory condition of the heart. It can be associated with a variable degree of morbidity and mortality.

Methods: We conducted an observational study to examine factors affecting survival in patients with sarcoidosis. Totally 122 patients with biopsy-proven sarcoidosis enrolled, underwent pulmonary function tests, a 12-lead electrocardiogram, an echocardiogram and a 24-hour Holter monitoring. Cardiac sarcoidosis was detected based on known criteria. All-cause mortality and cardiac death were the primary and secondary endpoints.

Results: During a median of 58.89±15.75 months follow-up, ten deaths (8.2%) were reported. The demographic characteristics of the survivor patients and those who died are presented in table 1.

Factors affecting mortality in sarcoidosis

<table>
<thead>
<tr>
<th>Factors</th>
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<th>Dead n=10/122 (8.2%)</th>
<th>Statistical significance</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>47.4±4.67</td>
<td>62.3±3±18.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TLC</td>
<td>85.4±6.12.97</td>
<td>57.3±7.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLCO</td>
<td>80.8±64.61.61</td>
<td>43.5±4±18.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean 24-hour HR</td>
<td>79.5±7.94</td>
<td>82.7±1.13.4</td>
<td>NS</td>
</tr>
<tr>
<td>SD24</td>
<td>122.5±81.16.08</td>
<td>77.8±1.18.88</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Five patients (4.1%) died due to cardiac causes. Cardiac involvement was detected in 40 patients (32.8%). The multivariate analysis showed age, standard deviation of RR intervals < 0.00 ms, TLC < 80% of the predicted, DLCO < 80% of the predicted and the cardiac involvement were independent risk factors of all-cause mortality.

Conclusion: The thorough evaluation of the results from a full cardiopulmonary monitoring in patients with sarcoidosis may be able to detect factors related with increased risk of mortality.

P3723 Long-term treatment with infliximab in patients with sarcoidosis

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Background: Long-term benefit and safety of infliximab treatment in patients with chronic sarcoidosis remain unclear. We wanted to assess clinical benefit and safety of long-term infliximab treatment in patients with chronic steroid-resistant sarcoidosis.

Methods: A retrospective chart review of all patients with chronic steroid-resistant sarcoidosis who received infliximab between January 2003 and November 2010. Pulmonary function tests and index lesions before and after infliximab therapy were assessed.

Results: 28 patients received infliximab, 16 of them for more than 12 months. 5 (31%) of these 16 patients with long-term infliximab treatment had a predominately pulmonary and 11 (69%) a predominantly extrapulmonary disease. Mean duration of treatment was 29 months (range 12 - 62). 6/11 (55%) patients with mainly extrapulmonary sarcoidosis showed a complete remission of their index lesion, 4/11 (36%) had a partial remission, and 1/11 (9%) showed no response. 1/5 patient with predominantly pulmonary sarcoidosis showed a >10%-improvement of percentage predicted forced vital capacity (FVC/P%); 3/5 showed a 0.10%-improvement, and in 1 patient FVC/P% declined. Thus, overall 14/16 (88%) patients profited from long-term infliximab treatment. Suspected adverse effects which lead to a temporarily discontinuation of infliximab therapy were noticed in 1/16 (6%) patient.

Conclusions: This retrospective study indicates that long-term infliximab is very efficient and safe in patients with chronic steroid-resistant sarcoidosis when assessed with individualized treatment targets. Patients with predominantly extrapulmonary sarcoidosis seem to profit more than patients with predominantly pulmonary disease.
15%, p<0.001). Extra-respiratory involvement of sarcoidosis was less frequent (21 vs 47%, p=0.04) in patients as well as residual granulomatous activity, as judged by serum angiotensin converting enzyme and HRCT signs. However, mortality was similar between the two groups.

Conclusion: The phenotype of patients with HC is original. An exposure to inhaled particles may play a role in the development of this particular fibrosis evolution and explain the local respiratory severity of sarcoidosis while the disease seems less active and severe from a systemic point of view.

P3726
Thyroid disease in an Irish cohort of sarcoidosis patients
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Introduction: Sarcoidosis is a multisystem disease of unknown aetiology with prevalence rates in the West of Ireland being among the highest in the world. Sarcoidosis is attributable to an altered or incomplete immune response to an auto- or alloantigen in genetically susceptible hosts. The association of sarcoidosis and thyroid disease has been described in numerous studies with a range of variability. Baseline prevalence rates for thyroid disease in the population range from 0.1 to 3%.

Objectives: The purpose of our study was to estimate the prevalence of thyroid disease in a cohort of sarcoidosis patients in the West of Ireland.

Methods: Using our patient database from 1983-2009, we retrospectively identified those who had thyroid function testing (TFTs) and reviewed the clinical indication, treatment and related physiological, radiological and treatment findings.

Results: 139/4907 (34.2%) had TITs. Of these, 24/139 (17.3%) were abnormal with 15/139 (10.7%) hyperthyroid and 9/139 (6.5%) hypothyroid. Mean age was 40.3yrs (median 37) with M:F ratio of 1.2. Mean time to diagnosis was 5.8yrs. There was no relationship with presentation, lung function, radiological stage or treatment of sarcoidosis. There was no association with hypercalcaemia, hypercalcuria, coeliac or other autoimmune disease.

Conclusion: We have demonstrated a moderately increased prevalence of thyroid disease on follow-up of Irish patients with sarcoidosis particularly in relation to hyperthyroidism. This is in contrast to Antonelli who reported a high prevalence of hyperthyroidism. This is in contrast to Antonelli who reported a high prevalence of hyperthyroidism. Further investigation is needed.

P3727
Pulmonary hypertension and right ventricular impairment in patients with sarcoidosis
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There is little date about frequency of pulmonary hypertension (PH) and right ventricular (RV) impairment in patients with sarcoidosis. In this work we examined the prevalence PH in these disorders using noninvasive cardiopulmonary evaluation. 33 patients (aged 50,64±2,8y) with sarcoidosis have been studied. 8 pts was with R I stage and 26 with IIIE stage of sarcoidosis. Criteria of exception were the clinical patients who had heart arrhythmia and heart heart hypertrophy. Control group was made 14 normotensive patients (aged 47,57±1,86). All patients were studied using realtime, phased array, two-dimensional Doppler echocardiography. The pulmonary artery systolic pressure (SP) was calculated as the sum of the transmucipudal pressure gradient and the right atrial pressure.

Methods: PH (SP>35 mm Hg) is revealed at 18 patients (52.9%) and 10 pts (30.3%) had SP > 40 mm Hg. Doppler-estimated SP at the patients with sarcoidosis exceeded SP at the healthy persons (p<0.001). RV hypertrophy was present in 84,8% patients (p<0.001 with controls). RV dilation was present in 90% patients with sarcoidosis (p<0.001). Right atrial diameter in patients with sarcoidosis was higher than at the healthy persons (p<0.001). RV wall in patients with sarcoidosis was higher than at the healthy persons (p<0.001). RV diameter in patients with sarcoidosis was higher than at the healthy persons (p<0.001). RV diastolic dysfunction we noted in 58.3% pts.

We noted a correlation between SP and MRS scale (r=0,52, p<0,01). RV diameter was present in 90% patients with sarcoidosis (p<0.001). Right atrial diameter in patients with sarcoidosis was higher than at the healthy persons (p<0.001). RV diastolic dysfunction we noted in 58.3% pts.

Conclusion: Pulmonary hypertension and right ventricular abnormalities is common in patients with sarcoidosis.

P3728
Clinical and morphological signs of liver damage in patients with pulmonary sarcoidosis
Marina Lebedeva1, Irina Popova1, Elena Popova2, Andrew Ponomarev2, Elena Arion3,4.1, Pulmonology, Moscow Sechenov Medical University, Moscow, Russian Federation; 2Pathology, Moscow Sechenov Medical University, Moscow, Russian Federation; 3Hepatology, Moscow Sechenov Medical University, Moscow, Russian Federation

The aim of our study was to identify clinical and morphological signs of liver damage in patients with pulmonary sarcoidosis.

Patients and methods: 65 patients with morphologically proved pulmonary sarco- idosis were examined. Pulmonary function testing, high-resolution CT (HRCT), liver tests were evaluated. Biopsy of lung (65), liver (52) were performed. Biopsy of liver were performed of the signs of cytolisis and/or cholestasis were present.

Results: 65 patients had markers of active pulmonary sarcoidosis: respiratory fail- ure which correlated with HRCT signs of activity such as ground - glass opaque (p<0.003) and morphology of specific granulomatosis. 52 patients also presented slight hepatomegaly, signs of cytolisis (AST 1,2-2,5 norms, ALT 1.3 - 2.7 norms) and/or cholestasis (GGT 1,6-3,4 norms) which correlated with morphological signs of liver granulomatosis: the non-casecting granulomas were in all biopsies, three types of histologic change were found: inflammatory (78%) cholestatic (51%), and vascular (19%). Inflammatory changes included inflammation suggestive of chronic active hepatitis. Among those with cholestasis, 9 had a pattern of perifiductal fi- brosis. Vascular changes consisted of sinusoidal dilatation (3 cases) and nodular regenerative hyperplasia (7 cases). No cirrhosis were found.

Conclusion: Liver involvement can be considered as a marker of extra-pulmonary activity in pulmonary sarcoidosis.

P3729
Diagnostic value of epithelioid cell granulomas in bronchoscopic biopsies
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Background: The granulomatous inflammatory response is a manifestation of many lung diseases.

Objective: To evaluate the diagnostic value of epithelioid cell granulomas in bronchoscopic biopsies in daily clinical practice.

Methods: The data of 157 consecutive patients with epithelioid cell granulomas in biopsy tissue who had undergone the bronchoscopic lung biopsy or bronchial biopsy were examined. All cases were divided into non-necrotizing epithelioid cell granulomas and epithelioid cell granulomas with necrosis.

Results: Of the all cases 108 had non-necrotizing epithelioid cell granulomas and 49 had epithelioid cell granulomas with necrosis. With respect to the presence of necrosis in granulomas, the majority of the patients had sarcoidosis or tuberculosis (34%). 95% of the patients with sarcoidosis had non-necrotizing epithelioid cell granulomas and the remaining 5% had granulomas with necrosis. The sensitivity of non-necrotizing epithelioid cell granuloma for the diagnosis of sarcoidosis was 95% and specificity 57%. The positive and negative predictive values were 69% and 92%, respectively.

Conclusion: A significant overlap in types of granulomatous inflammation between tuberculosis and sarcoidosis was found. The type of epithelioid cell granuloma alone was not sufficient for the final clinical diagnosis.

P3730
Is sarcoidosis associated with increased occurrence of malignancy? A retrospective analysis
Martina Doubkova, Ilona Binkova, Jana Skrickova. Department of Pulmonary Medicine, University Hospital Brno, Czech Republic

Background: There are few reports with ambiguous results concerning the rela- tionship between sarcoidosis and malignancies. The incidence and prevalence of malignancies in sarcoidosis patients with a malignancy was 68 years (44-75). The women:men ratio was 4:1. All patients were non-smokers. Median time from diagnosis of sarcoidosis to the malignancy was 6.5 years (0-14).

Methods: We performed a retrospective analysis in our cohort of 170 sarcoidosis patients. We compared the incidence and prevalence of malignancies in sarcoidosis patients with the incidence and prevalence of malignancies in the normal population (Czech Oncology Registry data). Data from years 2005-2007 were analyzed.

Results: The analysis only included patients with sarcoidosis diagnosed prior to malignancy, or patients with malignancy discovered simultaneously with sarcoidosis.

Results: Out of our sarcoidosis patients, 5 of them were diagnosed with malignant tumors (3 breast cancers, 1 colorectal carcinoma, 1 non-Hodgkin lymphoma). The median age of sarcoidosis patients with a malignancy was 68 years (44-75). The women:men ratio was 4:1. All patients were non-smokers. Median time from sarcoidosis diagnosis to malignancy was 6.5 years (0-14). Calculated prevalence of malignant diseases in patients with sarcoidosis was: 813/100000 (2005), 2379/100000 (2006), and 2941/100000 (2007). In the Czech population, the preva- lence of all malignant diseases between 2005-2007 was 3522-3856/100000. In patients with sarcoidosis, calculated incidence of malignancies in the monitored period was: 0 (2005), 2054/100000 (2006), and 588/100000 (2007). The incidence of all malignant diseases in the Czech Republic was 698-738/100000.

Conclusion: We do not prove the statistically significant difference in the inci- dence and prevalence of malignancies between sarcoidosis patients and general population.
P3731

QRS-T angle significantly increased in sarcoidosis patients

Elias Gualano1, Anastassia Kallianos2, Vasilios Koumanos1, Maria Ntouskou1, Eleni Takitou1, Elias Peros3, Lemonia Vlentza2, George Dionelis4, Charalampos Kostopoulos3, George Mathioudakis4, Ioannis Arapis1,2,3

1Department of Pathophysiology, Laiko Hospital University of Athens, Greece; 22nd Pulmonary Clinic, General Hospital of Chest Diseases “Sotiria”, Athens, Greece; 39th Pulmonary Clinic, General Hospital of Chest Diseases “Sotiria”, Athens, Greece; 4Pulmonary Clinic, General Hospital of Nikaiaka, Athens, Greece; 5Clinic of Thoracic and Cardiac Surgery, Alexandra General Hospital University of Athens, Athens, Greece

Introduction: Aim of the study was the evaluation of the QRS-T-angle, a novel marker of ventricular repolarization, in asymptomatic patients with sarcoidosis and investigation of the relationship between QRS-T-angle and occurrence of ventricular arrhythmias.

Methods: The ECG derived QRS-T-angle was calculated in 112 sarcoidosis patients. The QRS-T-angle was assessed compared to control groups, both subgroup analysis showed that patients with CI and Lown >3 had significantly elevated QRS-T-a.

Results: The ECG derived QRS-T-a of 112 sarcoidosis patients was calculated while cardiac involvement (CI) was assessed based on known criteria. Assessment of the ventricular arrhythmias was based on the Lown classification criteria. All patients were compared to 65 healthy controls. Results: 36/112 patients fulfilled the criteria of CI while 15 patients were classified as Lown 4A and 4B. The QRS-T-a of sarcoidosis patients was significantly increased compared to controls, while subgroup analysis showed that patients with CI and Lown >3 had significantly elevated QRS-T-a.

Electrocardiographic and clinical characteristics among the groups

<table>
<thead>
<tr>
<th>Non CI</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC&lt;3</td>
<td>LC≥3</td>
</tr>
<tr>
<td>(n=65)</td>
<td>(n=67)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128±14</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79±14</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74±14</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67±14</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>52±14</td>
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<td>Heart rate (bpm)</td>
<td>3±14</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>1±14</td>
</tr>
</tbody>
</table>

Conclusion: QRS-T-angle can be considered to be a marker of extra-pulmonary granulomatous lesions in sarcoidosis.

P3734

Serum angiotensin converting enzyme (ACE) as additional clinical markers of activity of pulmonary and extra-pulmonary locations of sarcoidosis

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1Department of Pulmonary Medicine, Moscow Medical University, Moscow, Russian Federation; 2Pathology, Moscow Sechenov Medical University, Moscow, Russian Federation

Introduction: Aim of the study was to identify additional clinical predictors of activity of extra-pulmonary locations in sarcoidosis patients.

Patients and methods: 107 patients with histologically proved pulmonary sarcoidosis were examined. Pulmonary function testing, high-resolution CT (HRCT), echocardiography, daily ECG monitoring, myocardial scintigraphy, renal tests were evaluated. Biopsy of lung (107), skin (74), kidney (13), liver (52) and heart (4) were performed. Biopsy of organs were performed if the suspected specific sarcoid organ failure. Serum concentration of ACE levels were determined with a spectrophotometric method.

Results: 57 patients presented sings of clinical and morphological activity of sarcoidosis (group 1), 50 without parameters of activity (group 2). Clinical and morphological signs of extra-pulmonary locations of sarcoidosis were in 32 active patients, in 7 – not active patients. Granulomas were found in skin (33,8%), heart -1, in liver (37,1%), in kidney (5 38%). Elevation of serum ACE were more in the 1st group: 63,7 (49,1- 79,8) micrograms/L vs 43,1 (32,5-47,2) micrograms/L in the 2nd group (p=0,0021). Level of serum ACE directly correlated with HRCT stage of activity as such as grade -opaque (p=0,0045) and morphology of specific granulomatous extra-pulmonary changes (p=0,0047).

Conclusion: Level of serum ACE can be considered to be a marker of extra-pulmonary granulomatous lesions in sarcoidosis.

P3735

Manifestations of malignancies during the course of sarcoidosis

Jelica Videnovic-Ivanov, Violeta Vucinic, Snezana Filipovic, Vladimir Zuzic, Jelena Stojic. Pulmonology, Clinic for Lung Diseases and Tuberculosis, Belgrade, Serbia

Introduction: Sarcoidosis is the granulomatous disorder with chronic course which can involve any organ in human body. Coexistence of two disorders is potential.

Method of the work: Analysis were retrospective. All patients with histologically proved sarcoidosis were obtained. Patients were ambulatory or hospital treated in the Clinic for lung diseases and tuberculosis. Malignancies were also histologically proved.

Results: Among 1307 patients with sarcoidosis (ACCES group, ERS) only 15 patients with malignancies were obtained. Mean ages were 47.3 years, and 11 F/4 M ratio was found. In 5 patients malignacies were the first obtained diagnosis in patients life as followed: carcinoma mammae (2 patients), carcinoma renis, fibrosarcoma and chronic leucemia. The mean time in which were made diagnosis was - 3.1 years. All patients were treated for carcinoma, till nowadays. In 11 patients, malignancies followed the sarcoidosis in mean time of 7.7 years. M. Hodgkin, adenocarcinoma ovarii, melanoma malignum, carcinoma cutis (3 female patients), adenocarcinoma intestine, carcinoma rect (2 patients), carcinoma mammae. Mean time of sarcoidosis duration was 8.3 years. All patients with sarcoidosis were medically treated even for relapses. In this group 3 lethal outcomes were obtained.

Conclusion: Coexistencies exists even in sarcoidosis. The question is what is the cause for manifesting sarcoidosis and malignancies. Is immunodefitenica one progression. Most studies of the effects of corticosteroids have concentrated on changes in chest radiograph and lung function (PFT). A recent systematic review (Paramothayan, S. et al. Respir Med 2008;102:1-9) found no studies that reported the effects of corticosteroids on symptom.

Objectives: To investigate whether corticosteroids were associated with improved PFT or symptom score (SS) over a 2-year follow-up.

Methods: PFT and SS before and treatment were compared with results at 3, 12 and 24 months in 20 patients given oral corticosteroids for active pulmonary sarcoidosis. To calculate SS dyspnoea was valued 1-5 by severity, and all other symptoms were valued at 1. Data were collected from clinical records and results evaluated using a 2-tailed paired t-test.

Results: 14 females and 6 males aged 29-63 years were included; 13 black, 6 Caucasian, 1 Asian. Initial symptoms included dyspnoea (11), cough (8), skin changes (9), arthralgia (8), eye problems (7). SS improved significantly at all time points. Improvement in PFT was not statistically significant.
of the potential factors in manifesting sarcoidosis and in manifesting malignancies. Another question is due to cytotoxic drugs delivering during the treatment from malignancies. One of the known cytostatics which can cause granulomatous disorders is vinblastin.

P3736

Experience of hydroxychloroquine in the treatment of pulmonary sarcoidosis in the west of Ireland: An insight into clinical practice

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Introduction: Hydroxychloroquine is widely used in treatment of cutaneous sarcoidosis. There is limited literature regarding the experience of hydroxychloroquine in pulmonary sarcoidosis.

Aims: To review the treatment and toxicity profile of hydroxychloroquine in treatment of pulmonary sarcoidosis.

Methods: Retrospective observational cohort study of sarcoidosis patients in the West of Ireland from 1983-2009. Remission was defined as successful withdrawal from steroids within one year, improvement in radiological staging of pulmonary disease (Scadding classification) and maintenance of pulmonary function. Relapse was defined as deterioration necessitating reintroduction of steroids.

Results: 92/407 (22.6%) were treated with hydroxychloroquine 200mg BD. Mean age 38.1yrs (range 17-68) with M:F ratio 1:1. Mean length of treatment 2.9yrs. Mean follow-up 8.5yrs. 19.6%, 47.8%, 25% and 7.6% had stage 1-4 disease respectively. 95.6% received high-dose steroids prior to treatment. Indications for treatment were: steroid-sparing 17.4%, refractory 18.5%, extra-pulmonary 47.8% and maintenance of remission 16.3%. 52.2% were steroid-free within one year; 23.9% showed improvement in radiological staging (normal radiology in 13%); there was no significant difference in lung function. Relapse rate was 14.1%. Adverse event rate was 11.9% (4.3% continued treatment).

Conclusion: This study shows hydroxychloroquine is safe and effective in the treatment of pulmonary sarcoidosis, particularly cutaneous. We conclude, therefore, that hydroxychloroquine should be considered in the treatment and maintenance of patients with chronic pulmonary sarcoidosis.

P3737

Characteristics of inflammatory bowel diseases-associated interstitial lung diseases

Camille Bron 1, Marianne Kambouchner 2, Thomas Gille 1, Yurdagul Uzunhan 1, Dominique Valeyre 1, Hilario Nunes 1.

Aim: To review the characteristics and pulmonary involvement of inflammatory bowel diseases (IBD) but most publications are limited to small series or predate the 2002 ATS/ERS statement on idiopathic interstitial pneumonias.

Methods: A retrospective review of 120 patients with HP seen at two centres from 1990 to 2010. Patients were classified according to the criteria of Schuyler and Cormier. CT scans were classified according to the Sahin et al score. Patients with chronic evolution of HP were compared to those with disease regression.

Results: We included 70 patients. Average age was 50 years: 65.7% females and 84.3% non-smokers. Avian proteins (81.4%) and moldy cork dust (7.1%) were the most common etiological antigens. Twenty-nine (41%) patients progressed to chronicity. Restrictive ventilatory syndrome was more severe in the group of patients with chronic evolution with lower FVC (p < 0.03), FEV1 (p < 0.05) and TLC (p < 0.02). Presence of reticular and honeycombing patterns were associated with evolution to chronicity (p = 0.003). The existence of centrilobular nodules was associated with regression of disease (p=0.011). The extension of radiological findings didn’t correlate with HP evolution.

Conclusion: No statistically significant differences between groups concerning BALF cellular- admixture.

P3738

Characterization of chronic hypersensitivity pneumonitis and evaluation of its predictive factors – Retrospective study

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1Pneumology Department, Hospital de Braga, Braga, Portugal; 2Pneumology Department, Hospital S. João, Porto, Portugal; 3Radiology Department, Hospital S. Joao, Porto, Portugal; 4Pathology Department, Hospital S. João, Porto, Portugal

Background: A percentage of patients with hypersensitivity pneumonitis (HP), despite appropriate therapeutic measures, evolves to chronicity. Objective: Characterization of clinical presentation, lung function, radiological, histological and bronchoalveolar lavage fluid (BALF) features of patients with chronic HP and evaluation of its potential predictive factors.

Methods: Retrospective analysis of patients with HP diagnosed according to the criteria of Schuyler and Cormier. CT scans were classified according to Sakin et al score. Patients with chronic evolution of HP were compared to those with disease regression.

Results: We included 70 patients. Average age was 50 years: 65.7% females and 84.3% non-smokers. Avian proteins (81.4%) and moldy cork dust (7.1%) were the most common etiological antigens. Twenty-nine (41%) patients progressed to chronicity. Restrictive ventilatory syndrome was more severe in the group of patients with chronic evolution with lower FVC (p < 0.03), FEV1 (p < 0.05) and TLC (p < 0.02). Presence of reticular and honeycombing patterns were associated with evolution to chronicity (p = 0.003). The existence of centrilobular nodules was associated with regression of disease (p=0.011). The extension of radiological findings didn’t correlate with HP evolution.

Conclusion: No statistically significant differences between groups concerning BALF cellular-admixture.
**Results:** The lungs of all cases showed pathologically some stage of diffuse alveolar damage (DAD) coincident with the period after acute exacerbation. In 11 cases, several stages of DAD were recognized in the lungs of same patient. DAD is found exclusively in the area without honeycombing. Although 5 cases showed also bud-type intra-alveolar fibrosis, which composed of accumulated myofibroblasts with few vessels and occasionally connected with ring-like DAD fibrosis. We do not reach the conclusion that they were OP or AIP. In addition to DAD, fibrosis which was frequently observed in 9 cases including the walls of honeycombing. The activity of IFP itself was estimated to be high in these patients.

**Conclusions:** The pathologic findings of acute exacerbation are DAD, and the several stages of DAD are characteristically observed in the same patient, which are similar to DAD caused by drug injury.

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**P3741**

**Interstial lung disease associated by gemcitabine chemotherapy in non-small lung cancer patients: Analysis based on the data in practical use with confirmed denominator**

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**Internal Medicine. Division of Pulmonary Medicine Infection and Oncology, Nippon Medical School, Tokyo, Japan**

**Background:** Gemcitabine (GEM), which is often used for non-small cell lung cancer (NSCLC), was reported to induce interstitial lung disease (ILD) in Japan. Presently, all-case postmarketing surveillance was to be generally conducted after the launch of new anti-cancer drug to investigate less-frequently but serious adverse drug reactions such as ILD in Japan. However, all-case surveillance had not been conducted for GEM and there is few data of GEM-induced ILD incidence in NSCLC patients with GEM chemotherapy in single institute.

**Methods:** We conducted a retrospective observational study of all NSCLC patients who received GEM in our hospital through medical records.

**Results:** We reviewed chemotherapy for NSCLC with GEM. ILD developed in five (2.9%) among these patients. ILD developed 10 to 80 days after the first administration of GEM. Of the five patients, four patients improved by steroid, whereas one patient died due to disease progression. The characteristics of the patients showed to be as risk factors of drug-induced ILD, such as age, performance status, and smoking history, concomitant use of anti-cancer drugs, were compared between ILD and non-ILD patients. However, significant differences were not detected.

**Conclusions:** Incidence rate of GEM-associated ILD in NSCLC patients was 2.9% in this study. Most of the patients who developed ILD had a good prognosis but one of them had a fatal outcome. We weigh the difference between our result and previous reports of GEM-associated ILD.

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**P3742**

**Lymphoid hyperplasia and eosinophilic pneumonia as histologic manifestations of amiodarone-induced lung toxicity**

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**Background:** Amiodarone use is often limited by lung toxicity. Amiodarone lung disease (ALD) classically manifests as organizing pneumonia with intra-alveolar foamy macrophages, but other patterns may occur. Herein we report two previously unreported patterns of ALD, lymphoid hyperplasia (LH) and eosinophilic pneumonia (EP).

**Method:** We identified patients with LH or EP as a prominent feature among 75 cases of probable ALD from the authors’ teaching files collected from 1997-2010. Clinical history and wedge biopsies were reviewed.

**Results:** Twelve patients (7 men) met inclusion criteria. Median age was 71 years. Amiodarone dose was known in 10 cases (median 200mg/d). Treatment duration was known in 8 cases and ranged from 1 to 9 years. Thoracic imaging showed diffuse infiltrates concerning for ALD. Histologic review revealed intra-alveolar foamy macrophages in all cases. Eight cases prominently displayed patterns of LH including diffuse LH (7), follicular bronchiolitis (5), lymphocytic interstitial pneumonia (2), and lymphocytic perivascular cuffing (2). Two showed features of acute EP including diffuse alveolar damage with abundant eosinophils. Two showed features of chronic EP including interstitial pneumonia with abundant eosinophils, patchy organization, fibrous exudates, and interstitial thickening. One chronic EP case also showed focal LH. Additional features included intra-alveolar giant cells (6), pleuritis (3), small poorly-formed granulomas (3), and thrombi (2).

**Conclusions:** Lymphoid hyperplasia and eosinophilic pneumonia are previously unrecognized histopathologic manifestations of ALD, and amiodarone exposure should be included in their differential diagnosis.

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**P3743**

**Concomitant Interferon-gamma 1b have a role in treatment of fibrosing NSIP?**

Barbara Bellfotore, Marialiusa Bocchino, Giuseppe Antinolli, Antonio Ponticelli, Roberta Di Grazia, Alessandro Sanduzzi Zamparelli, Sepideh Nikfam.

**Clinical and Experimental Medicine, Respiratory Diseases, Naples, Italy**

**Aim:** To detect the effectiveness of Interferon-gamma 1b in patients with fibrotic NSIP.

**Methods:** We reviewed clinical records and pathologic findings of 11 patients with IFP (all males, mean age 54.2±6.3 yrs), who underwent surgical biopsy and were treated with IFN-gamma 1b between 2005 and 2007. In all patients, before therapy, after 6 and 12 (T2) months of treatment, the following parameters had been measured: lung volumes, DLCO, mPAP estimated and reclassified according to the ATS/ERS consensus classification of interstitial pneumonia.

**Results:** 5 out of 11 patients, previously diagnosed as Usual Interstitial Pneumonia, after the revision were identified as fibrotic NSIP. In 5 patients, ILD was reviewed for GEM and there is few data of GEM-induced ILD incidence in NSCLC patients who received GEM in our hospital through medical records.

**Conclusion:** Incidence rate of GEM-associated ILD in NSCLC patients was 2.9% in this study. Most of the patients who developed ILD had a good prognosis but one of them had a fatal outcome. We weigh the difference between our result and previous reports of GEM-associated ILD.

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**P3744**

**The clinical dynamic changes and prognosis analysis in patients with cryptogenic organizing pneumonia**

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**Background:** Cryptogenic organizing pneumonia (COP) is a common subtype of Alveolar Proteinosis (AP) which has a multivariate clinical feature.

**Objectives:** To characterize the clinical dynamic changes and to identify predictive factors for relapse of patients with COP.

**Methods:** COP patients who received COP x-ray were diagnosed in our hospital from Jan 1,1998 to Oct 1, 2009 and followed up until Mar 31, 2010.

**Results:** 1) 78.5% (57/73) patients with subacute onset responded well to steroid. No improvement showed significant improvement during the first three months. 2) Consolidation, ground glass opacity and reticular shadow were three most common abnormal patterns on CT scan during the early stage of the disease. Ground glass opacity (GGO) could progress into consolidation, later, in turn, inverted into GGO and then resolved completely after corticosteroid treatment. Ground glass opacity showed rapid and significant resolution after the treatment. Reticular shadow resolved slowly. 4) 25.7% (17/73) patients went through relapses. 70.6% (12/17) relapses occurred during the first year after the treatment while the steroid is stopped or tapered (<10mg/d).

**Conclusions:** 1) COP runs a benign course and shows a significant improvement on pulmonary function test and Chest CT in response to steroids. 2) Relapses occur frequently when steroid is tapered (≥10mg/d) or stopped, mostly during the first year. Relapses do not affect the outcome. 3) Decreased diffusing capacity and hypoxemia maybe important predictors of the relapses and tapering too fast may increase the risk of relapse.

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**P3745**

**Follow up 1 year of amiodarone pulmonary effects**

Galina Orlova, Julya Nikolaeva, Larisa Kiruchina, Aleksandra Speranskaya, Vitaliy Perley, Aleksey Gikhin. Laboratory of Environment and Occupational Pulmonology, Scientific Research Institute for Pulmonology I.P.Pavlov’s State Medical University, Saint-Petersburg, Russian Federation

**Amiodarion has numerous side-effects and the pulmonary toxicity (PT) is the most serious.**

**Aim:** To analyse the therapeutic prognosis of amiodarone-induced PT (AIPT). 14 AIPT patients (mean age 66.0±12.2 y) received amiodarone (300-400 mg/day) for 47.6±3.5 months due to cardiac arrhythmia, were investigated. X-ray, computer tomography (CT), complex lung function examination, echodopplercardiography were performed. All patients discontinued the amiodarone and received prednisolone (60-20 mg/day) with gradual tapering up to 10-5 mg/day for 6 months. Lung biopsy was done in 2 cases and confirmed interstitial pulmonary fibrosis.

**Results:** AIPT was diagnosed over 2.7 yr after the clinical manifestation. The onset of AIPT was acute in 3, subacute in 8, insidious in 2 cases at 2 frequencies. The frequency of CT signs were: interstitial - 1.0, nodule - 0.22, and infiltrative or “ground glass” - 0.88. Restrictive type of functional disorders (0.91), pulmonary hypertension 33.7±1.8 mm Hg and cor pulmonale (0.57) were revealed. In 2 cases it was amiodarone-induced thireoiditis. After 1 yr therapy the improvement of clinical (0.83) and CT (0.83) signs, lung functional tests (DLCO, p<0.05; VC, p<0.005; RV, p<0.001; DLCO, p<0.05) were observed. The rapid decrease of prednisolone dose in 2 cases lead to the clinical and CT deterioration.

**Conclusion:** The corticosteroid treatment of AIPT is of therapeutic value and must be prolonged with carefully tapering to avoid the deterioration.
Combined pulmonary fibrosis and emphysema. Descriptive analysis from a specialized clinic of interstitial lung disease
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The combination of pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome characterized with pulmonary fibrosis (PF) and emphysema.

Aim: To analyze the clinical, functional, radiological and echocardiographic features in patients with CPFE.

Method: Prospective study conducted in a specialized clinic of ILD from 01/01/2007 to 31/12/2010. PF was defined as reticulopapilae with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis without ground glass opacities in HRCT and emphysema as the presence of areas of low attenuation with a very thin or no wall and/or bullae with upper zone predominance.

Results: We anlzied 20 patients; 90% men; mean age 74 years; 91% were smokers or ex-smokers, 60% had dyspnea, 75% basal crackles and 25% finger clubbing. The pulmonary function tests are shown in table 1. Pulmonary hypertension was detected in 5 of 10 patients who underwent echocardiography.

### Pulmonary function tests in 20 patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC %</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>FEV1% pred</td>
<td>86</td>
<td>18</td>
</tr>
<tr>
<td>FVC % pred</td>
<td></td>
<td>90</td>
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<tr>
<td>TLC % pred</td>
<td>81</td>
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<tr>
<td>RV % pred</td>
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<tr>
<td>RV/TLC % pred</td>
<td>104</td>
<td>24</td>
</tr>
<tr>
<td>TLCO % pred</td>
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<td>46</td>
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<tr>
<td>PaO2 at rest</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>6 Minute Walking Distance</td>
<td>455</td>
<td>96</td>
</tr>
<tr>
<td>SpO2 at exercise</td>
<td>84</td>
<td>8</td>
</tr>
</tbody>
</table>

SD: standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; TLCO: transfer factor for carbon monoxide; PaO2: partial pressure of oxygen in arterial blood; SpO2: arterial oxygen saturation.

Conclusions: The finding of lung volumes normal or minimally altered in contrast to a severe reduction in TLCO and arterial hypoxemia should alert to the possibility of CPFE. The prevalence of PH in these patients is high.

The King's sarcoid questionnaire (KQ): The development of a novel health related quality of life (HRQOL) questionnaire
Amit Patel1, Richard Siegert1, Akin Sowemimo1, Daniel Creamer4, Genevieve Larkin5, Athol Wells3, Irene Higginson2, Surinder Birring1.

Health related quality of life (HRQL) is impaired in sarcoidosis. Fatigue, pain, cough, breathlessness, visual disturbance and appearance of skin lesions are common concerns of patients. There is a paucity of validated disease specific tools to assess HRQOL of patients with sarcoidosis. We set out to develop a sarcoidosis specific HRQOL questionnaire. Items were generated from patient interviews (n=23), review of literature and a multi-disciplinary team meeting. A modular questionnaire was recommended because of the multisystem nature of sarcoidosis. A preliminary questionnaire consisted of 65 items and a 7 point Likert response scale. The preliminary King’s Sarcoid Questionnaire (KQ) was tested in 205 patients (184 lung, 55 skin, and 45 eye disease) at two sites (King’s College Hospital and the Royal Brompton Hospital). The following items were removed: 1) floor effect >60% of participants responded “rarely” or “never” (8 items), 2) inter-item correlations of ρ<0.8 (12 items), 3) items that did not fit unidimensional scales following Rasch analysis (11 items). The King’s Sarcoid Questionnaire (KQ) comprises of 5 modules: general QOL (12 items), lung (8 items), medication and side-effects (3 items), skin (4 items) and eyes (7 items). The KQ is currently undergoing evaluation of test-retest reliability and responsiveness to change.

Evaluation of the COPD assessment test (CAT) for measuring health-related quality of life in patients with interstitial lung disease
Kazuma Nagata, Keisuke Tomii, Michio Hayashi, Kojiro Otsuka, Ryo Tachikawa, Kyoko Otsuka. Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan.

There is a need for a short, simple, and well validated instrument to assess health-related quality of life (HRQL) in patients with interstitial lung disease (ILD). The study was conducted to evaluate the validity of the COPD assessment test (CAT), which is a newly developed short and simple questionnaire for COPD with good measurement properties, in ILD. 52 ILD patients completed the CAT and the St. George’s Respiratory Questionnaire (SGRQ). The patients also completed the MRC dyspnea scale, the Leicester Cough Questionnaire (LCQ), and the Hospital Anxiety and Depression Scale (HADS) and also underwent a six-minute walk test, pulmonary function tests, and arterial blood gas analysis.

The correlation between the CAT score and the SGRQ total score was very strong (r=0.93, p<0.0001). The CAT score was also significantly correlated with the SGRQ symptoms score (r=0.74, p<0.0001), with the SGRQ activity score (r=0.87, p<0.0001), and with the SGRQ impact score (r=0.89, p<0.0001). Stepwise multiple regression analysis demonstrated that the MRC score and the LCQ score were the most strongly contributing factors to both the CAT score and the SGRQ total score. The CAT is a short and simple questionnaire for assessing ILD health status with good measurement properties.

Fungal colonization in interstitial lung diseases
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Background: Many of interstitial lung disease are tend to impair the immunity, thus patients in this group have a higher risk of fungal diseases. But still little is known regarding the role of fungal colonization in interstitial lung diseases, when fungus are not define a causative agent.

Aim: To investigate the incidence and effects of fungal colonization of lower respiratory tract using PCR of bronchoalveolar lavage (BAL) specimens among patients with sarcoidosis and extrinsic allergic alveolitis (EAA).

Materials: 132 patients with sarcoidosis, and 80 patients with EAA undergo BAL with further PCR test for A. fumigatus and C. albicans using commercial assays. Cytology of BAL, different disease parameters including functional tests, radiology were analyzed.

Results: In sarcoidosis patients, Aspergillus was found in 22 cases (16.7%), 14 were males, and Candida detected in 11 cases (8.3%) -3 were males. Among EAA patients, Aspergillus detected in 13 cases (16.2%), 5 were males, and Candida in 9 (11.3%) cases, 4 were males. In sarcoidosis, Candida colonization was associated with lower FVC (72%), DLCO (64%), and higher neutrophils level in BAL (32%), as also disease duration (112.8 weeks) vs patients without it (92%, 88%, 9% and 18.2 weeks, respectively). In EAA Candida detection was also associated with lower DLCO (58%), 6-minute walk test distance (340 m), higher neutrophils level in BAL (34%), disease duration (107.3 weeks) vs patients without it (72%, 421 m, 12% and 48.7 weeks, respectively). Aspergillus detection altered disease parameters in similar way.

Conclusion: Colonization of respiratory tract with fungi in interstitial lung diseases plays a prominent role in deterioration of disease.

Forced vital capacity decreases rapidly in patients with idiopathic upper lobe-dominant pulmonary fibrosis
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We present five patients with upper lobe-dominant pulmonary fibrosis of unknown etiology that does not fit any of the currently defined subsets of idiopathic interstitial pneumonias. We describe the clinical, functional, and pathological characteristics of this disorder, which we have provisionally termed idiopathic upper lobe-dominant pulmonary fibrosis (iULPF).

All patients were slender, with a body mass index of 16.0–17.9 kg/m2. Four of the five patients had recurrent pneumothorax. Their pathological characteristics were as follows: 1) upper lobe-dominant subpleural proliferation of elastic fibers associated with deposition of mature collagen in alveolar lumens; 2) isolated fibrotic areas to less-involved pulmonary parenchyma; and 5) destruction of the lung architecture.

Evaluation of the COPD assessment test (CAT) for measuring health-related quality of life in patients with interstitial lung disease
Kazuma Nagata, Keisuke Tomii, Michio Hayashi, Kojiro Otsuka, Ryo Tachikawa, Kyoko Otsuka. Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan.

There is a need for a short, simple, and well validated instrument to assess health-related quality of life (HRQL) in patients with interstitial lung disease (ILD).
P3751 Pulmonary hypertension and right ventricular impairment in patients with interstitial pneumonia
Nina Karol, Andrea Brebow. Hospital Therapy Department, Saratov State Medical University, Saratov; Russian Federation
There is little data about frequency of pulmonary hypertension (PH) and right ventricular (RV) impairment in patients with idiopathic interstitial pneumonia (IIP). In this work we examined the prevalence PH in these disorders using noninvasive cardiological examination. A total of 40 patients (aged 50±3.2±5.5) with IIP have been studied in early period after IIP diagnosed. Criteria of exception were the clinical displays heart disease, arterial hypertension. Control group have made 14 normotensive volunteers (aged 47±7±1.86). All patients were studied using realtime, phased array, two-dimensional Doppler echocardiography. The pulmonary artery systolic pressure (SP) was calculated as the sum of the transmural pressure gradient and the right atrial pressure.
Results: Pulmonary hypertension (SP > 35 mm Hg) is revealed in 15 patients with IIP and SP > 40 mm Hg – at 7 (17.5%). Doppler-estimated SP at the patients with IIP exceeded SP at the healthy persons (p < 0.001). RV hypertrophy was present in 23 (57.5%) patients (p < 0.001). RV dilation was present in 76.5% patients with IIP (p < 0.001). RV diastolic dysfunction was revealed in 65% patients. Right atrial diameter in patients with IIP was significantly higher than at the healthy persons (p < 0.001). RV wall in patients with IIP was significantly higher than at the healthy persons (p < 0.001). RV diastolic dysfunction revealed in 56% pts. We noted correlations between SP and dyspnoe intensity (scale MRS) (r = 0.63, p < 0.01), VC (r = 0.61, p < 0.01), VC = (r = 0.39, p < 0.01), FEVI = (r = 0.38, p < 0.01), SaO2 (r = 0.58, p < 0.01).
Conclusion: Pulmonary hypertension and right ventricular abnormalities is common in patients with IIP.

P3752 Interstitial lung diseases in Europe
Roberto Carbone1, Rosangela Filiberti2, Riccardo Ghio1, Gregor S. Zimmermann1, Katharina Jakob 1, Werner von Wulffen1, Rainer Baumgartner3, Juergen Behr4, Claus Neurohr1.
Aim: ILD would be important to the planning of services for these patients, but so far nevertheless they constitute 15-20% of all respiratory pathologies as compared to 6-25% in Europe, ILD incidence rates ranged from 3.62 (South of Spain) to 7.6 cases × 100,000 inhabitants (Spain) according to different studies. In the majority of cases a male predominance was found. Among ILD, the most frequent entities were idiopathic pulmonary fibrosis (IPF: 19-39% of all ILD), sarcoidosis (12-35%) and hypersensitivity pneumonia (3-12%). Incidence rates of IPF and sarcoidosis ranged from 0.93 (Greece) to 6.78 cases × 100,000 (UK) and from 1.07 (Greece) to 5.59 × 100,000 (UK), respectively. Median age at diagnosis was about 61 years for IPF and 42 years for sarcoidosis. Fibrotic NSIP was considered as a new subgroup, making up 20-35% of patients previously diagnosed as IPF. Few data exist on the frequency of ILD and discrepancies among different areas have been observed. Differences in fact but are due to the use of disomogeneous sources (disease registries, selected clinical series, different study designs), to the incidence of outbreak or prevalent cases, to variable criteria for diagnosis, or to selection bias.

P3753 Effect of PDE-5 inhibitor treatment in patients with interstitial lung disease and pulmonary hypertension
Gregor S. Zimmermann1, Katharina Jakob1, Jens Geiseler2, Julia Fresenius2, Hanno H. Leuchte3
Methods: English articles on ILD epidemiology in Europe were reviewed using PubMed as the search engine.
Results and conclusions: In Europe, ILD incidence rates ranged from 3.62 (South of Spain) to 7.6 cases × 100,000 inhabitants (Spain) according to different studies. In the majority of cases a male predominance was found. Among ILD, the most frequent entities were idiopathic pulmonary fibrosis (IPF: 19-39% of all ILD), sarcoidosis (12-35%) and hypersensitivity pneumonia (3-12%). Incidence rates of IPF and sarcoidosis ranged from 0.93 (Greece) to 6.78 cases × 100,000 (UK) and from 1.07 (Greece) to 5.59 × 100,000 (UK), respectively. Median age at diagnosis was about 61 years for IPF and 42 years for sarcoidosis. Fibrotic NSIP was considered as a new subgroup, making up 20-35% of patients previously diagnosed as IPF. Few data exist on the frequency of ILD and discrepancies among different areas have been observed. Differences in fact but are due to the use of disomogeneous sources (disease registries, selected clinical series, different study designs), to the incidence of outbreak or prevalent cases, to variable criteria for diagnosis, or to selection bias.

P3754 Pulmonary hypertension in patients with interstitial lung disease
Zeynep Dogan1, Sinan Ergenli1, Husseyn Yildirim1, Gumulu Ak1, Ragip Ozkan2, Fusun Alatas1, Muazzfer Metinbas1. 1Department of Chest Disease, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey; 2Department of Radiology, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey
Pulmonary hypertension (PH) is commonly seen in patients with interstitial lung disease (ILD), and is associated with a worse prognosis. The aim of this study was to determine the prevalence and characteristics of PH in patients with ILD. Demographic and clinical characteristics, physiological studies, six minute walking test (6MWT) and high resolution computed tomography (HRCT) results were prospectively collected, and compared between patients with and without PH. Pulmonary hypertension was defined by right heart catheterization as mean pulmonary artery pressure > or = 25 mm Hg and pulmonary artery occlusion pressure < or = 15 mm Hg.
The study cohort consisted of 30 patients. The final diagnoses of these patients were idiopathic pulmonary fibrosis (IPF) (24 (80%) cases), asbestosis (2 (7%). Background: Interstitial lung diseases (ILD) comprise a disomogeneous group of more than 200 pulmonary disorders and are progressive life-threatening diseases. Etiology is unknown in a variety of ILD. ILD are considered rare diseases, nevertheless they constitute 15-20% of all respiratory pathologies as compared to 6-25% in Europe, ILD incidence rates ranged from 3.62 (South of Spain) to 7.6 cases × 100,000 inhabitants (Spain) according to different studies. In the majority of cases a male predominance was found. Among ILD, the most frequent entities were idiopathic pulmonary fibrosis (IPF: 19-39% of all ILD), sarcoidosis (12-35%) and hypersensitivity pneumonia (3-12%). Incidence rates of IPF and sarcoidosis ranged from 0.93 (Greece) to 6.78 cases × 100,000 (UK) and from 1.07 (Greece) to 5.59 × 100,000 (UK), respectively. Median age at diagnosis was about 61 years for IPF and 42 years for sarcoidosis. Fibrotic NSIP was considered as a new subgroup, making up 20-35% of patients previously diagnosed as IPF. Few data exist on the frequency of ILD and discrepancies among different areas have been observed. Differences in fact but are due to the use of disomogeneous sources (disease registries, selected clinical series, different study designs), to the incidence of outbreak or prevalent cases, to variable criteria for diagnosis, or to selection bias.

P3755 Resting PaO2 and 6MWT as diagnostic index for nocturnal oxygen desaturation in diffuse parenchymal lung diseases
Sheetu Singh1, Manan Lal Gupta2, Ravinder Singh2, Virendra Singh 2. 1Chest & Tuberculosis, SMS Medical College, Jaipur, Rajasthan, India; 2Pulmonary Medicine, SMS Medical College & Hospital, Jaipur, Rajasthan, India
Introduction: Despite of normal daytime oxygen saturation many patients of diffuse parenchymal lung disease (DPLD) desaturate during night time. Such patients may develop signs of pulmonary arterial hypertension (PAH) which increases the mortality and morbidity in DPLD. The aim of this study was to determine the magnitude of nocturnal oxygen desaturation and find its predictors in DPLD. Methods: It was a cross sectional and observational study. 48 consecutive patients of DPLD were recruited. Idiopathic pulmonary fibrosis (IPF) was diagnosed by ATS/ERS guidelines 2002 and other DPLD by their clinical and radiological presentation. Arterial blood gas analysis, six minute walk test (6MWT) and overnight pulse oximetry were done and variables such as time spent with nocturnal oxygen saturation (SpO2) below 90%, mean SpO2, worst SpO2 and apnea - hypopnea index were recorded. Results: Amongst 48 subjects, 35 (72.9%) patients had IPF. 9 (18.8%) patients had hypersensitivity pneumonitis and 4 (8.3%) patients had stage 4 sarcoidosis. Nocturnal desaturation (>10% of sleep time with SpO2 <90%) was observed in 20 (41.7%) subjects. The desaturators were found to have resting daytime PaO2 of less than 61mm of Hg (p=0.0015), end SpO2 after O2 <83.5% (p=0.0077) and distance walked during 6MWT ≤380.4m (p=0.0051). Based on cut off values of these variables an index called desaturation index was evolved which had 95% sensitivity. Conclusion: Significant nocturnal oxygen desaturation occurs in many patients of DPLD despite of normal resting SpO2. A desaturation index based on PaO2 and SpO2 after 6MWT and distance walked during 6MWT was found to be 95% sensitive in diagnosing nocturnal desaturators.
Drug induced lung disease: 11 cases
Eld Kupeli, Yucge Sahin Ozenmirel, Zeynep Ezryzun Ozen, Gaye Ulubay, Sule Akcay, Fusun Oner Eynoboglu. Pulmonary Diseases, Baskent University School of Medicine, Ankara, Turkey.

Drug induced lung disease (DILD) is the most common cause of iatrogenic damage to the lungs. More than 350 drugs have been identified leading to DILD. We evaluated the characteristics of patients with DILD between 2007-2010, at our institution retrospectively, for demographic features, pulmonary function tests (PFTs), diffusion capacities, high resolution computed tomograms (HRCT) findings, diagnostic methods and treatment modalities. 11 patients (M/F=9:2, mean age 60±20.3) were identified with DILD. 3 had chronic myeloid leukemia; congestive heart failure, asthma, testicular cancer, malignant melanoma, acute lymphocytic and myelocytic leukemia, renal transplantation and lung cancer was diagnosed in one patient each. Cough, respiratory failure and fever were the most common symptoms. 4 patients exhibited normal, 5 revealed restrictive, one patient for each revealed obstructive and mixed PFTs. Diffusion capacities in 6 patients were low. Ground glass opacities (2), bilateral patchy consolidation (2), interstitial fibrosis (2), pleural effusion (1) were evident in HRCT, however 1 patient revealed no abnormality. 3 patients underwent bronchoscopy for bronchosclerotic lavage. Infections causes were excluded by microbiological and laboratory tests. Lung involvement was thought to be due to bleomycin (1), methotrexate (1), cyclophosphamide (1), cisplatin (1), dasatinib (2), Ara-C (2), ciclosporin (1), amiodaron (1), tacrolimus (1). Radiological and clinical improvement was achieved with systemic steroids in 10 and cessation of the drug in one. DILD can cause significant mortality and morbidity. We believe that consequence of DILD could be reduced by high degrees of suspicion and by excluding other causes for common pulmonary symptoms and abnormal radiographic findings.

Quadriceps function is reduced in fibrotic idiopathic interstitial pneumonia
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Introduction: Little is known about the quadriceps function and its role in exercise capacity in Fibrotic Idiopathic Interstitial Pneumonia, FIP.

Methods: To compare quadriceps function in patients with FIP and healthy controls and relate it to exercise capacity, 25 patients with FIP, FVC 78.7% predicted and 25 sex and age matched healthy controls were studied. Measurements included FFM, respiratory muscle strength, voluntary quadriceps strength (QMVC), twitch quadriceps force (TwQ), an endurance protocol of 5 min. Both groups had comparable anthropometrics and respiratory muscle strength. Quadriceps force declined more rapidly in patients in the endurance protocol. TwQ was lower in patients.

Conclusions: Patients with FIP have significantly impaired quadriceps strength and endurance. In contrast to controls, quadriceps function is not correlated with 6MWD.

Assessment of cardiac involvement in patients with sarcoidosis
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Background: Cardiac involvement remains an important prognostic factor in patients with sarcoidosis. However, early diagnosis of cardiac sarcoidosis has been difficult because the clinical manifestations are not specific and the sensitivity and specificity of the diagnostic modalities are limited.

Methods: Patients with biopsy proven sarcoidosis were prospectively recruited from the outpatient clinic of sarcoidosis and underwent a full cardiological monitoring including pulmonary function tests, echocardiography, cardioangiography, a 24-hour ambulatory ECG and cardiac magnetic resonance imaging (MRI) when appropriate. Cardiac involvement was assessed based on known established Japanese Ministry of Health (JMH) criteria and on modified criteria using MRI as a major criterion for cardiac sarcoidosis. All consecutive patients were followed for 5 years for major adverse events.

Results: Seventy patients (43 female) were enrolled with median age 49.96±12.83 years old and disease duration 4.4±4.5 ±27 years. Cardiac involvement was identified with the modified criteria in 27 patients (38.5%) while 10 (14.3%) patients were found based on the JMH criteria, showing a more than two-fold higher rate for the MRI group (p=0.005). On follow-up, 9 patients had adverse events including 5 cardiac deaths. All patients with cardiac cause of death had cardiac sarcoidosis based on the modified criteria.

Conclusion: Evaluation of myocardial involvement in sarcoidosis with the use of MRI as a major criterion appears to be more sensitive than current consensus criteria and associated with future adverse events including cardiac death. Cardiac MRI evaluation may be of great importance in the early diagnosis of cardiac sarcoidosis.

Prognostic significance of serum markers in acute exacerbation of idiopathic interstitial pneumonias
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Introduction: Acute exacerbation (AE) of idiopathic interstitial pneumonias (IIPs) is a topic for recent years. We have shown that diffuse pattern of high resolution CT (HRCT) at AE of idiopathic pulmonary fibrosis (IPF) is a worse prognostic factor (Akira, AJRCCM 2008). Prognostic significance of serum levels of KL-6 and surfactant protein (SP)-D in AE of IIPs has not been clarified sufficiently.

Aim: We examined clinical findings in AE of IIPs retrospectively to clarify the significance of serum KL-6 and SP-D as a prognostic factor.

Methods: Seventy cases of AE of IIPs were diagnosed according to the guideline of Japanese Respiratory Society in 2004 and classified with radiological and/or pathological findings into two groups: IPF (n=55) and non-IPF (n=15).

Results: Serum levels of KL-6 and SP-D were compared between 30days survivors and non-survivors. Prognostic factors determining 30 days survival was examined by logistic regression analysis among various clinical parameters including serum markers, HRCT patterns at AE (diffuse/non-diffuse).

Results: Serum SP-D levels of 30 days survivors at AE were significantly less than that of non-survivors, however, there was no difference in serum KL-6 levels. Serum KL-6 of patients with diffuse pattern was significantly lower than that of patients with non-diffuse pattern. Logistic analysis revealed that serum KL-6 at AE, white blood cell counts, immunoglobulin G, gender, complication of diabetes mellitus and pre-treatment before AE were significant factors determining 30 days survival.

Conclusions: Serum KL-6 (>1450U/ml) is a significant worse prognostic factor determining 30 days survival in AE of IIPs.
How often do respiratory specialists agree with the diagnosis of COPD made in general practice? An audit of referrals to a community based COPD centre (BreathingSpace) in the UK

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The Rotherham BreathingSpace (BS) is a nurse-led community based centre for the delivery of specialist care for Chronic Obstructive Pulmonary Disease (COPD). BS agreed with GP diagnosis of COPD in 27/37 (73%) of cases and management showed some improvements in quality between 2007 and 2008 but highlighted the current UK Quality and Outcomes Framework used in general practice assessed only the quantity and not the quality of spirometry. The purpose of this audit was to assess the reliability of the diagnosis of COPD made in general practice when referred on to a specialist respiratory service (BS). A retrospective review of a random sample of COPD patient referral forms (N=398, 207 males and 191 females) sent to BS from general practice between May 2007 and Sept 2009 was undertaken. 213 (54%) of these referrals had spirometry measured on the referral (mean FEV1 % = 54, FEV1/FVC= 0.59). Of the completed assessments the services are provided by GP diagnosis of COPD in 27/37 (73%) of patients and disagreed with the COPD diagnosis in 64 (19%) of patients. The BS non COPD diagnoses were Asthma (N=30, 9%), Restrictive lung disease (N=20, 6%), non obstructive Emphysema (N=4, 2%), Bronchiectasis (N=2, 0.6%) and no respiratory disease (N=20, 6%).

These findings suggest that 4 out of 5 COPD diagnoses made in general practice referred to our centre (BS) are reliable but there is still room for improvement. Further education and quality improvement is recommended in COPD diagnosis in line with national guidelines.

A survey of pulse oximeter use by general practitioners in East Berkshire, UK

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Introduction: The importance of measuring oxygen saturation in primary care is highlighted in many national guidelines, such as asthma (Thorax 2008; 63(Suppl 4):i121), community acquired pneumonia (Dx 2009; 64(Suppl 3):i153-55), Chronic Obstructive Pulmonary Disease and guidance on the use of emergency oxygen. Pulse oximeters are cheap, portable, and easy to use, but it is unclear whether they are widely utilized in the community setting.

Methods: Questionnaires were sent to all 54 general practitioner (GP) surgeries in the region - requesting information about their pulse oximeter use and opinions of their clinical value. A response from all practices was achieved by making telephone contact in the event the questionnaire was not returned.

Results: Twenty-one (39%) of the 54 surgeries did not own a pulse oximeter. Of these, 6/21 (29%) said they would not find one useful, and had no future intention of purchasing one. Ten of these 21 surgeries (48%) were keen to obtain one, but the main barriers to this were cost and the time required to research the market. The inner-city surgeries were less likely to have one – 8/17 (47%) inner-city surgeries vs. 25/37 (68%) outside the city. Of the 33 surgeries that did have an oximeter, 89% found them clinically very helpful, and the majority had just one machine (24/33 – 73%).

Conclusions: Over a third of GP surgeries do not own a pulse oximeter – despite clear indications for their use in the assessment of patients with respiratory illness. Highlighting these indications to GPs, in addition to outlining their relative low cost and ease of use may increase the popularity of this monitor of the “fifth vital sign” in primary care.

Using population insight studies to define effective prevention and identification interventions in COPD

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Background: In England over 3 million people are living with COPD. Only 835,000 are diagnosed usually at the more severe end of the disease spectrum. The national COPD programme highlighted the need for strategies both to prevent and identify COPD earlier in order to fundamentally change the disease burden and improve quality of life.

Objectives: To establish optimum approaches to promote positive lung health behaviour and symptom recognition by individuals and populations at risk of COPD.

Methods: An extensive literature review was undertaken together with stakeholder interviews to identify reasons for limited popular awareness of COPD and under-stand the impact of behaviour change interventions. Focus groups and interviews with informants in priority population segments were used to derive and test insights into effective approaches.

Results: Behaviour change interventions in COPD are more effective if targeted on priority population segments. Collaboration with charities and commercial organisations can help to identify and engage people at risk. Behaviour change interventions should be tailored to the individual and the population segment. Measurement of lung age may increase likelihood of stopping smoking. For those who are healthy but at risk, messages should be positively framed around lung health. For those with symptoms, negative message framing around lung disease may be more effective in changing behavior.

Conclusions: Interventions tailored to the individual and population segment are more likely to be effective in changing behaviour. The results of this segmentation and insight work have informed the approach in England to the prevention and early identification of COPD.

Poor quality of health services at primary care level is the leading cause of uncontrolled asthma in India

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Background: Due to inadequate health resources in India the peripheral health services are not able to provide services as per the guidelines –GINA especially in the case of uncontrolled practitioners and GP. There is need to educate the practitioners particularly those at the periphery about the guidelines for asthma management.

A novel study design to assess the utility of the COPD assessment test (CAT) in improving asthma in India

Kevin Gruffydd-Jones1, Helen Pearce2, Steve Holmes3, Peter Kardos4, Roger Escamilla5, Roberto Dal Negro6, Jane Roberts1, Gilbert Nadeau2, David Leather2, Paul Jones8, Box Surgery, Box, Corsham, United Kingdom; 2Respiratory Centre of Excellence, GlassSmithKline, London, United Kingdom; 3Park Road Surgery, Shepton Mallet, Somerset, United Kingdom; 4Gemeinschaftspraxis und Zentrum für Pneumologie, Allergologie, Schlafmedizin, Klinik Maimaug, Frankfurt, Germany; 5Service de Pneumologie, Hôpital Larrey-CHU Toulouse, Toulouse, France; 6Divisione di Pneumologia, Ospedale Civile Orlando di Bussolengo, Bussolengo, Verona, Italy; 7Clinical Sciences Building, Salford Royal Hospital Foundation Trust, Salford, United Kingdom; 8Clinical Sciences, St George’s University of London, London, United Kingdom

Background: CAT is a new, patient completed, questionnaire designed to provide a simple and reliable measure of health status in COPD. The CAT has been validated against other measures of quality of life and outcomes of COPD (Jones P et al, EJR 2009;34:648-54). However, its ability to improve the dialogue between patient and physicians has not been evaluated. We set out to design a study to assess the impact of CAT on the quality of the consultation between a primary care physician (PCP) and COPD patient.

Methods: The CAT in Primary Care Study is a randomised, parallel group study conducted in 5 European countries. 160 PCPs without a working knowledge of CAT are recruited to the study. Each PCP completes 6 videoed consultations with standardised COPD patients (professional actors). PCPs are randomised to the CAT arm: with patient notes and CAT available in the consultations; or the non-CAT arm: with just the patient notes available.

Cases were developed to include usual patient issues, which the actors were trained not to proactively raise with the PCP. The cases and their CAT scores were independently verified.

Assessments are conducted by independent physicians. Each assessor will review 4 test cases for benchmarking. The assessments are based on the PCPs ability to

Measurement of lung age may increase likelihood of stopping smoking. For those who are healthy but at risk, messages should be positively framed around lung health. For those with symptoms, negative message framing around lung disease may be more effective in changing behavior.

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PO363 Novel study design to assess the utility of the COPD assessment test (CAT) in improving asthma in India

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identify, understand and manage the patient issues (A) and whether they reviewed key typical COPD issues (B). The primary endpoint of the study is the comparison of the assessment score (AvB) between the arms. The study has >90% power to detect a 3 point (out of 40) difference between the arms. A pilot study was successfully conducted with 10 PCPs to confirm the feasibility of the study. The study is ongoing and results are expected late 2011.

P3765

The Breathing Bus – A primary care model for identifying undiagnosed COPD in hard to reach populations. A pilot study

June Roberts1, Helen Allsop2, Nizar Harb3, Tjard Schermer1.

Aims: To identify the number of undiagnosed COPD and to signpost to general practice for further assessment

Methods: A mobile health bus was sited in areas of high SED with good footfall and accessibility. Nurses trained to recognise COPD symptoms, perform FEV6 micro-spirometry and experienced in informal, non-medicalised approaches to health and disease staffed the bus. High risk individuals (over 35 yrs, smoker or ex-smoker with symptoms suggestive of COPD) were targeted for FEV6 micro-spirometry. Consent was gained to share all results with own GP. Those with unexplained respiratory symptoms and/or abnormal FEV6 readings were asked to see their GP for further assessment. Follow up with patient experience survey took place two months after the bus.

Results: The bus visited 6 sites on 7 occasions. 350 people visited the bus: between 6% and 87% of contacts were from areas of high SED. Of 119 in the high risk group, 67% men and 45% females had symptoms suggesting COPD of those suitable for FEV6 readings 30% of men and 38% women had airflow obstruction: all were signposted to their GP. 48% were current smokers. Data from the experience survey indicates that many suspected something was wrong; accessibility and convenience prompted them to come forward for testing.

Conclusion: Our pilot work suggests that mobile units in non-clinical settings can increase accessibility to SED groups and prompt high risk individuals to be tested for COPD. Further work is needed.

P3766

Two year mortality of COPD in primary care in Greece: An observational study

Kostas Marinis, Ioanna Verou-Katsarou, Panthera Mystridou, Eleni Apostolidou, Haragio Patsouras, Konstantinos Georgoulakis. Respiratory Medicine Department, University of Thessaly Medical School, Larissa, Greece

Introduction: COPD remains a significant cause of death worldwide. However, in primary care in Greece there is still a large proportion of undiagnosed COPD patients. Parameters associated with mortality in COPD patients have not been identified.

Aims and objectives: To assess the parameters associated with two year mortality in newly diagnosed COPD patients in primary care in Greece

Methods: Using an open spirometry programme, 118 newly diagnosed COPD patients were identified over two years. Phone contact was performed every six months, whereas the study participants were examined and categorized by the mobile health bus.

Results: The bus visited 6 sites on 7 occasions. 350 people visited the bus: between 6% and 87% of contacts were from areas of high SED. Of 119 in the high risk group, 67% men and 45% females had symptoms suggesting COPD of those suitable for FEV6 readings 30% of men and 38% women had airflow obstruction: all were signposted to their GP. 48% were current smokers. Data from the experience survey indicates that many suspected something was wrong; accessibility and convenience prompted them to come forward for testing.

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P3767

Exhaled nitric oxide: A useful adjunct test in assessing asthma control in primary care – A cross-sectional exploration

Eveline Termeer1, Jiska Sneek-Stroband2, Hanneke Nuiten1, Persijn Honkoop2.

Aim: To explore the consequences of omitting FeNO as an adjunct to symptoms and spirometry for assessing asthma control in primary care.

Methods: We performed a cross-sectional analysis of two available cohorts of adult asthmatics. We assessed FeNO, lung function and Asthma Control Questionnaire (ACQ) levels in all participants. Pearson correlation coefficients were calculated between FeNO, ACQ, %FEV1 predicted and reversibility. In a scenario analysis, patients' asthma control was categorized according to two established control markers, and FeNO as an extra marker.

Results: We included 147 and 160 patients (in total 63% female; mean age 35.4). Correlations between FeNO, symptoms and lung function were weak (max 0.240, between FeNO and %FEV1). All three control markers were consistent in interpretation of asthma control in 25.7% of the population. In 28.1% symptoms and lung function were consistent but FeNO was contradicting and in another 46.3% the two established markers were contradictory. FeNO, symptoms and lung function in adults with asthma in primary care, which confirms that FeNO is an independent marker in assessing asthma control. In almost half the population, results of symptoms and lung function were contradicting regarding assessing asthma control; in this group FeNO may fine-tune categorization of asthma control.

P3768

A pilot study to detect airflow obstruction in smokers using spirometry in a local GP surgery

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COPD is under diagnosed worldwide. In our locality, it is thought that a fifth of all COPD cases have been identified.

Aim: To carry out a pilot study to screen smokers and ex-smokers in a local GP practice with spirometry to allow earlier COPD diagnosis.

Methodology: Over a 7 month period, subjects were identified from a GP practice database. The target population included smokers/ex-smokers over the age of 35 who had smoked a minimum of 10 pack years; recurrent or chronic respiratory symptoms; occupational exposure to respiratory irritants or family history of COPD. Patients known to have COPD or asthma were excluded.

Appropriate subjects completed a short questionnaire to screen smokers and ex-smokers in a local GP practice with spirometry to allow earlier COPD diagnosis.

Conclusion: We observed weak correlations between FeNO, symptoms and lung function in adults with asthma in primary care, which confirms that FeNO is an independent marker in assessing asthma control. In almost half the population, results of symptoms and lung function were contradicting regarding assessing asthma control; in this group FeNO may fine-tune categorization of asthma control.

P3769

Effectiveness of supervised training program about spirometry in primary care

Crystina Represas-Represas, Virginia Leiro-Fernández, Maribel Botana-Rial, Ana Isabel González-Silva, Alberto Fernández-Villar. Pneumoology, Respiratory and Infectious Disease Research Group, Bio-Medical Research Institute of Vigo, University Hospital Complex of Vigo (CHUVI), Vigo, Pontevedra, Spain

Spirometry is an essential technique for diagnosing respiratory diseases but it is underused at Primary Care (PC) level. Training could help to improve the situation.

Objectives: To analyze the effectiveness of 2 months supervised training program about spirometry performance and interpretation.

Methodology: Interventional study, with measurements before and after, to improve the quality. Target population: doctors and nurses team, of 26 PC centers. Teachers: pulmonologists from our hospital (CHUVI). We designed a structured program showed in figure 1. To assess the effectiveness of the course, students were evaluated with a test-exam composed of 5 spirometries with 2 questions each one, at three different times: before initial training (test 1), at the end of the first working day (test 2), and on the 2nd working day (final test).

Results: Of 74 students, 72 (97.2%) completed training and 90% passed the exam. The mean punctuation in the different tests were: 4.1±0.1, 6.5±1.3 in test 1; 7.5±1.6 in test 2 and 8.9±1.3 in the final test (p<0.0001). The number of supervised spirometries performed and interpreted correctly was 370 of 521 (71%) during the first month and 562 of 619 (91%) during the second month (p<0.0001).

680s
Figure 1

Conclusions: An spirometry training program based on theoretical and practical workshops, and practical monitoring improves significantly the competence of PC professionals in the performance and interpretation of this technique.

P3770

Agreement between asthma control perception by patients, by physicians and according to guidelines

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Background: Despite the clinical interest and current treatments availability, more than a half of Spanish asthma patients fail to control their disease adequately.

Objective: To assess the degree of correlation between the asthma control perceptions by patients and by physicians.

Methods: Observational, cross-sectional and multicenter study that included patients with severe persistent asthma according to Spanish Guidelines for Asthma Management (GEMA). We calculated the degree of agreement between asthma control perceptions by patients, physicians and according to the GEMA.

Results: A total of 343 patients were included. Mean age (SD) was 48.1 (14.7) years and 1/3 were women. The assessment of the degree of asthma control according to GEMA criteria showed that only 10.2% of patients were controlled, 57.7% partially controlled and 22.1% poorly controlled. The correlation between patient’s asthma control perception and according to GEMA criteria showed that 35.7% of patients that viewed themselves under control did not achieve GEMA criteria (p < 0.0001). The agreement between physicians and GEMA criteria showed that 16.6% of asthma patients who reached medical criteria for control, were not under the GEMA control assumptions (p < 0.0001). Concordance between medical criteria and patient’s perception showed that only 57.9% of cases coincided for the control of asthma, while 40.7% of patients who felt controlled were not under physician opinion (p < 0.0001).

Conclusions: Both patients and physicians overestimate asthma control, with higher control perception in patients.

P3771

Peak flow is not strictly comparable by gauge and spirometry in many patients

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Peak Flow, usually measured by meter or gauge (PEFm), is commonly used in monitoring airway calibre in asthma and in COPD. Spirometry is increasingly used in COPD assessment in primary care. Most spirometers generate flow-volume curves yielding peak flow measurements (PEFvfl) which may also be used in monitoring patients. It is unclear how closely PEFm and PEFvfl relate in practice.

We determined PEFvfl (from 2 reproducible loops) using the Zen 100 spirometer and PEFm (best of 3 blows by Wright gauge) in 100 consecutive patients undergoing routine lung function.

General agreement between the 2 measures was good: mean PEFvfl was 333 (SD 139), mean PEFm was 317 (SD 137) L/min. However, PEFm was 20 L/min or more lower in 45 patients and 20 L/min or more higher in 12 patients than PEFvfl.

The 2 measures differed by 40 L/min in 27 patients.

Simple visual inspection of F-V loops did not predict the difference between the 2 measurements. Larger differences did not occur in asthma or COPD patients than in others or correlate with airflow obstruction.

In this small study the order of measurements was not randomised and the population may not be generalisable but clinically significant differences were apparent in a large proportion of patients using the different techniques. PEF measurements in an individual should preferably be compared using the same equipment. Lung function laboratories should determine both PEFm and PEFvfl.

P3772

Composite asthma control measures in real-life studies

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Background: Using real-life databases to compare asthma treatments requires composite proxies for asthma control.

Methods: Observational study using the US Ingenix Normative Healthcare Database to compare asthma outcomes between matched patients either initiating or increasing inhaled corticosteroid (ICS) therapy as fluticasone propionate (FP) or extra-fine hydrofluorokalene beclomethasone dipropionate (EF HFA-BDP). Literature-based a priori-defined composites were developed and evaluated over 1 yr, including: markers of emergency healthcare use for asthma and lower respiratory tract infections; use of oral steroids and reliever therapy; increased maintenance therapy, and controller-reliever ratio. Medication possession ratio (MPR) was calculated to assess adherence.

Results:

<table>
<thead>
<tr>
<th>Composite Measure</th>
<th>EF HFA-BDP</th>
<th>FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma control achieved (n, %)</td>
<td>348 (54.4)</td>
<td>348 (54.4)</td>
</tr>
<tr>
<td>Asthma control achieved + SABA (n, %)</td>
<td>271 (42.3)</td>
<td>271 (42.3)</td>
</tr>
<tr>
<td>No severe exacerbations, n, %</td>
<td>222 (68.9)</td>
<td>222 (68.9)</td>
</tr>
<tr>
<td>Decreased controller-reliever ratio (≥0.5, n, %)</td>
<td>271 (42.3)</td>
<td>271 (42.3)</td>
</tr>
<tr>
<td>MPR, %</td>
<td>30 (11.3)</td>
<td>30 (11.3)</td>
</tr>
<tr>
<td>Outcome year ICS dose, μg/day</td>
<td>44 (22-88)</td>
<td>27 (13-145)*</td>
</tr>
</tbody>
</table>

Conclusion: While the proportion of patients achieving asthma control varies according to the considered criterion, data consistently show similar or better outcomes for EF HFA-BDP despite a significantly lower ICS daily dose and similar MPR. Using multiple composite measures to evaluate comparative effectiveness reinforces confidence in study findings.

P3773

Pharmacists and knowledge of asthma: Survey of 120 pharmacists, comparison between 1999 and 2009

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Asthma morbidity has changed over the ten last years, we speculated that pharmacist knowledge concerning the treatment of asthma has also changed over years.

Aim: To compare pharmacists’ knowledge in asthma treatment in urban and rural areas between 1999 and 2009.

Material and methods: 120 pharmacists (60 licensed and 60 assistants) from the Bas-Rhin (North part of Alsace) were randomly selected on two occasions. The 2009’s pharmacists were all different from the 1999’s ones. 80 of them accepted to answer the same standardized questionnaire in 1999 and in 2009.

Pharmacists’ populations in 1999 and in 2009 were identical (age, gender, pharmacy location (urban vs rural), ...). Emergency interventions for an asthma attack were performed by 10.6% of them in 1999 and 8.6% in 2009 (NS). 33% of them advised patients to go back home after intervention in 1999 and 57% in 2009. They gave advice to obtain a better compliance (96% the two years) and explained how to use an inhaler (96% in 1999 and 94% in 2009) in the same proportion. Ten years later, 98% voluntarily demonstrated use of different inhalers instead of 64% in 1999 (p<0.05) (MDI, Autohaler, Turbuhaler) 14 and 9% knew how to use an MDI properly, 5% and 4% an Autohaler and 31 and 24% a Turbuhaler in 1999 and 2009, respectively (I don’t understand this point well).

Time spend per prescription was the same in the two years (< 15min).

* p<0.05

Conclusions:

- pharmacy location (urban vs rural), ...
- Difference in asthma treatment required between 1999 and 2009.
- Pharmacists populations were the same in 1999 and 2009.

681s
Conclusion: During the last 10 years, pharmacists knowledge about asthma has not increased significantly. On the other hand they were more prone to use an inhaler for a demonstration. Training pharmacists about asthma seems still necessary.

P3774
Know it, check it, treat it – COPD consumer mobilisation campaign. A pilot study
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Background: COPD is under diagnosed and awareness amongst the public is low. Aims: To develop and pilot a consumer mobilisation campaign* to increase public awareness of COPD and encourage the undiagnosed local population to recognise symptoms and present for further assessment.

Methods: Insights into attitudes to COPD and motivators/barriers to health messages were collected through focus groups with local clinicians and members of the public. Key messages were communicated using a variety of media over a 3-month period. Pre and post campaign awareness amongst clinicians and the public was measured using market research techniques.

Results: Key insights from focus groups:
Don’t focus on smoking. “We don’t like anti-smoking messages”
Get people to join the dots between their symptoms and COPD - “It’s only just dawned on me that my cough is not normal”
Make the message personal - “COPD may mean you become dependent on others” was a message that shocked people and would more likely prompt action.
Make statistics real – “1 in 7 people registered more with the target audience than 3.7 million people have the disease”
Of 75 people surveyed post launch:
Prompted awareness of COPD increased by 24% and its symptoms by 9%
Of 25 general practices surveyed post launch:
Awareness of the campaign amongst clinicians was high (80% unprompted)
There was an average increase in diagnosis rates of 2 patients per practice prompted by the campaign (range 0.15)

Conclusion: COPD consumer mobilisation campaigns can increase public awareness and diagnosis rates. Further work is needed.

Campaign developed and funded by Boehringer Ingelheim Ltd and Pfizer Ltd in collaboration with NHS Saltford

P3775
Knowledge of pulse oximetry among general practitioners in south Australia
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Aims and objectives: The feeling of satisfaction with inhaler (FSI-10) is a self-completed questionnaire designed to assess the patient opinions regarding the satisfaction and usability of the inhalers irrespectively of the drug used. It consists of 10 questions, each with 5 possible responses on a 5-point Likert scale scored from 5 to 1, respectively.

Objective: The aim of this study was to validate the Greek version of this questionnaire.

Methods: We performed an open, non-interventional, multicentre, parallel clinical study. The final group consisted of 422 subjects (192 females) aged between 16 and 87 years, who suffered from asthma or COPD and who regularly received their treatments exclusively via the inhaled route. All had already achieved mastery of their devices and they completed in full the Greek FSI-10 which had been translated by two specialists and back translated by another specialist. Statistical analysis was done by using SPSS version 17.0.

Results: The Greek version of the FSI-10 was easily understood and completed by the participants. Spearman’s rho correlation coefficients showed good relationships between questions and a positive contribution of the score of each question to the total score. No redundancy was observed. Cronbach test for the questionnaire as a whole showed a very good internal consistency (Cronbach’s alpha=0.923). Lower u values (0.907 - 0.922) were calculated, if any one of the items was consecutively deleted.

Conclusions: The reliability of the Greek version of the FSI-10 questionnaire was proven for the first time by this study. The instrument fits its purpose very well and can be used in multicentre clinical trials conducted in Greece.

P3777
Lung function disorders screening among the smoking patients in primary health care
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Background: Smoking is a major risk factor for chronic obstructive pulmonary disease (COPD). Prevalence of smoking in Russian Federation is one of the highest in the world: 39.1% of the adult population. The airflow limitation is not necessarily accompanied by certain symptoms and therefore some patients do not always seek for medical advice.

Aim: Early detection of airflow limitation and identification of risk factors for COPD among smoking patients in general practice in Northwest Russia.

Methods: 414 volunteers (smokers and ex-smokers) were invited to make the standardized lung function test and fulfilled the questionnaires (including the symptoms and smoking status). COHb% and carbon monoxide (CO) in exhaled air were established by MicroCO analyzer.

Results: Mean age was 42.1±13.6 years, 62.3% of the sample was males, and 80% of subjects were current smokers. The average smoking history was 25 pack-years for males and 14.8 for females. Subgroups of potential (smoking>10 pack-years) and high (> 25 pack-years) risk of COPD were defined (68.1% and 30.7%, respectively). The high levels of CO and COHb (>3%) were revealed in 25.5% and 35.9% smokers, respectively. The cough and dyspnoea were the main complaints (49.0% and 45.7%, respectively). Obstructive ventilation disorders were identified in 41.1% of subjects. The prevalence of obstruction increased with age and smoking history (p<0.001). Reversibility test was performed in 72% of all patients with identified disorders of lung function. COPD was detected in 28 patients (6%).

Conclusions: Early diagnosis of lung function disorders in smoking patients is an opportunity to identify individuals with increased risk of developing COPD.

P3778
The prevalence of respiratory infections in vaccinated patients with chronic obstructive pulmonary disease
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Aim: To estimate the prevalence of respiratory infections in immunized patients with chronic obstructive pulmonary disease (COPD).

P3776
Reliability of the FSI-10 questionnaire for the assessment of the usability of inhalers in Greek patients
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Introduction: The Feeling of Satisfaction with Inhaler (FSI-10) is a self-completed
It is important to continue working to get a proper diagnosis and treatment. Only 252 (6%) had a previous history of atopy. 1,960 (49.3%) had a family history of asthma. 921 (22.1%) were normal body mass index according to WHO classification. 2550 (60.9%) were non-smokers. Only 1369 (34.9%) did not complain of dyspnea (MRC = 0). We included 4,188 patients diagnosed with asthma, of which 2450 (60.2%) had been treated with an inhaled drug (bronchodilator and/or inhaled corticosteroid). All patients signed informed consent. Results: We included 4,188 patients diagnosed with asthma, of which 2450 (60.2%) were men. The mean age was 50.5 years (SD 17). 1486 patients (36.6%) had a normal body mass index according to WHO classification. 921 (22.1%) were non-smokers. 188 (4.5%) were current smokers. 1663 (41.4%) were sensitized to at least one allergen. 2528 (63%) of patients had rhinitis and 1,214 (30.3%) had a previous history of atopy. 1,960 (49.3%) had a family history of asthma. Only 1369 (34.9%) did not complain of dyspnea (MRC = 0). 2550 (60.9%) were treated with a combination of an inhaled corticosteroid and a long acting beta-2 agonist. Only 855 (20.6%) of patients who were diagnosed with asthma had a spirometry at any time prior to inclusion in the study and only 252 (6%) had a reversibility test. The mortality in vaccinated against influenza and pneumonaeus was 0.1%. However, the quality of life seems to be affected because of exacerbations and hospitalization which discomfort a significant percentage of COPD patients.

**P3779**
Evaluation of lung function on asthma patients cared by primary care physicians
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**Aim:** To know the characteristics of patients diagnosed as asthma in primary care.

**Methods:** Multicenter epidemiological, transversal and observational study performed in patients diagnosed as asthma in primary care and treated with an inhaled drug (bronchodilator and/or inhaled corticosteroid). All patients signed informed consent.

**Results:** We included 4,188 patients diagnosed with asthma, of which 2450 (60.2%) were women. The mean age was 50.5 years (SD 17). 1486 patients (36.6%) had a normal body mass index according to WHO classification. 921 (22.1%) were non-smokers. 188 (4.5%) were current smokers. 1663 (41.4%) were sensitized to at least one allergen. 2528 (63%) of patients had rhinitis and 1,214 (30.3%) had a previous history of atopy. 1,960 (49.3%) had a family history of asthma. Only 1369 (34.9%) did not complain of dyspnea (MRC = 0). Only 855 (20.6%) of patients who were diagnosed with asthma had a previous history of atopy. 1,960 (49.3%) had a family history of asthma. Only 1369 (34.9%) did not complain of dyspnea (MRC = 0). 2550 (60.9%) were treated with a combination of an inhaled corticosteroid and a long acting beta-2 agonist. Only 855 (20.6%) of patients who were diagnosed with asthma had a spirometry at any time prior to inclusion in the study and only 252 (6%) had a reversibility test. The mortality in vaccinated against influenza and pneumonaeus was 0.1%. However, the quality of life seems to be affected because of exacerbations and hospitalization which discomfort a significant percentage of COPD patients.

**Conclusions:** The mortality in vaccinated against influenza and pneumonaeus patients seems to be negligible. However, the quality of life seems to be affected because of exacerbations and hospitalization which discomfort a significant percentage of COPD patients.

**P3780**
Non-invasive ventilation (NIV) in community-acquired pneumonia (CAP) and severe acute respiratory failure (ARF): Effectiveness and risk factors for failure and mortality
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**Background:** The use of NIV for treating severe ARF due to CAP is controversial, and the risk factors for failure with this mode of ventilation are not well-known in these patients.

**Methods:** Prospective observational study to assess the usefulness of NIV in patients with CAP and severe ARF. The primary end-point variable was to determine the success of NIV, defined as avoidance of endotracheal intubation and survival in the ICU and for at least 24 hours in the medical ward, in patients with CAP. We assessed predictors of NIV failure and hospital mortality in multivariate analyses.

**Results:** We studied 184 consecutive patients with CAP and severe ARF: 102 (55%) patients had de novo ARF and 92 (45%) previous pulmonary or cardiac disease. NIV was successful in 116 (63%) patients. Hospital mortality was 10% (95%) in successfully treated patients and 37 (54%) in those who failed treatment (p<0.0001). The variables independently related to NIV failure in the multivariate analysis were SAPS-II at admission, maximum SOFA during NIV, older age, higher heart rate and lower PaO2/FiO2 ratio after 1 hour of NIV, and worsening of radiologic infiltrate 24 hours after admission. Likewise, independent predictors of hospital mortality were maximum SOFA during ICU stay, NIV failure and older age.

**Conclusions:** Patients with CAP and severe ARF can be treated with NIV with a reasonable success rate. Successful NIV treatment is strongly related with improved outcome in these patients. Multi-organ failure and older age strongly predict both treatment failure and poor survival.

**P3781**
Pressure support in acute hypercapnic respiratory failure in an acute clinical setting
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**Introduction:** Non-invasive ventilation (NIV) is now routinely used for treatment of Acute Hypercapnic Respiratory Failure (AHRF). There is much debate as to whether usage of higher pressures for ventilation improves the outcome in an acute setting.

**Aim:** We set out to assess what pressures for NIV were needed to achieve reversal of acidosis in AHRF in an acute clinical setting and what was the outcome.

**Method:** A scientific survey was conducted over 6 years in a teaching hospital ward-based NIV unit. Levels of Inspiratory Positive Airways Pressure (IPAP) and Expiratory Positive Airways Pressure (EPAP) levels needed to achieve reversal of acidosis in AHRF were analysed. Patients with AHRF were divided into 2 groups; AHRF from chronic obstructive airways disease (COPD) and AHRF from non-COPD related illnesses. Mortality during the admission in the 2 groups was also assessed.

**Results:** A total of 1188 episodes with 820 COPD related and 366 non-COPD related AHRF admissions were recorded. In the COPD group pressures (in cm H2O) needed for reversal of acidosis were IPAP max 30, min 10 and median 16.7; EPAP max 12, min 4 and median 5.2. In the non-COPD group; IPAP max 30, min 10 and median 16; EPAP max 11, min 4 and median 5.3. 318/20 (10.1%) of COPD and 50/366 (13.6%) of non-COPD patients died during admission.

**Conclusions:** Our findings suggest that reversal of acidosis AHRF from underlying COPD or other illnesses can be achieved with satisfactory outcomes without the need of high pressure ventilation. Further well designed studies would be needed to explore this further.

**P3782**
Home versus intensive care ventilators providing noninvasive ventilation (NIV): A clinical comparison during acute respiratory failure due to COPD exacerbation
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**Background:** Different bench test studies were performed to compare the performance characteristics of home and ICU ventilators. However little data in comparison are available in a clinical setting.

**Aim:** To compare the clinical effects of NIV delivered by ventilator dedicated to ICU versus devices designed for home care.

**Material and method:** We enrolled 30 patients admitted in semi-intensive care unit to AECOPD due to AECOPD (Baseline pH 7.24±0.04, PaCO2 87.4 mmHg ±16.5, PaO2 70.6 mmHg±18.9, aged 79.7 y, RR 36±9 y). 37% of patients were randomized in two groups to receive NIV delivered by an ICU ventilator or three home ventilators. Baseline characteristics showed no significant differences in both groups. Several exclusion criteria were included (i.e. coma, obesity, COPD or other illnesses can be achieved with satisfactory outcomes without the need of high pressure ventilation. Further well designed studies would be needed to explore this further.)

**Conclusions:** Home and ICU ventilators are equally effective in improving blood gas exchange. Further clinical studies could help clinicians in choosing the appropriate devices, tailoring the choice to a given patient.

**P3783**
Predictors of mortality in patients treated with non-invasive ventilation for acute hypercapnic respiratory failure due to COPD
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**Background:** Mortality in patients treated with non-invasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) during an acute exacerbation of COPD (AECOPD) is high. For many patients, AHFR is an end-stage process and NIV may be inappropriate. However there is no definitive method of identifying patients who are unlikely to survive.

**Aim:** The aim of study was to identify clinical and laboratory variables predictive of mortality in patients treated with NIV for AHRF due to COPD.
P3784 Non invasive ventilation (NIV) in conscious sedation with remifentanil
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Background: NIV use in acute hypercapnic respiratory failure (AHRF) patients who refused orotracheal intubation is an open question. Agitation is a frequent reason of NIV failure. Aim: We have evaluated the safety and tolerance of NIV in patients under conscious sedation induced by remifentanil.

Methods: Thirty (11F/19M) consecutive COPD patients with AHRF admitted to our Semi-intensive care Unit were unable to tolerate NIV treatment. Patients were submitted to conscious sedation (continuous sedation at random). We assessed the changes in arterial blood gas, tolerability and adverse events at the time of admission, after 30 min and 60 min of NIV use. Results: Pao2/Fio2 ratio improved after 60 min (p < 0.001). PaO2 increased from 46±7 (pre-NIV) to 61±4mmHg (post-NIV). PaCO2 decreased from 67±4 (pre-NIV) to 45±3 mmHg (post-NIV). We documented hypotension in 2 patients (7.6%) treated by dose adjustments. No bradycardia and respiratory depression were observed. We have not documented any unforeseeable event. No patient died during admission.

Conclusions: In selected population remifentanil is well tolerate in AHRF patients treated with NIV.

P3785 Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD
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Background: Endotracheal intubation (ETI) and mechanical ventilation are often needed in patients with acute-on-chronic respiratory failure (ACRF) due to acute exacerbations of COPD (AECOPD).

Purpose: It was to assess the usefulness of non invasive ventilation as an early extubation and weaning technique in ACRF secondary to AECOPD.

Patients and methods: Among 384 consecutively intubated patients admitted for AECOPD due to AECOPD, a prospective, randomized controlled trial of weaning was conducted in 264 patients who failed a 2-h spontaneous breathing trial, although they met simple criteria for weaning. Conventional invasive pressure support ventilation (IPSV) was used as the control weaning technique in 130 patients (IPSV group), and NIV was applied immediately after extubation in 134 patients (NIV group).

Results: No statistical difference was found in the characteristics of the two groups at randomization. In the IPSV group, 100 of 130 patients were successfully weaned and extubated, versus 124 of 134 in the NIV group (p < 0.05). NIV like IPSV significantly and similarly improved gas exchange in relation to that achieved during a 2-h spontaneous breathing trial (p < 0.05). The duration of ETI was significantly shorter in the NIV group (4.52±0.87 d) than in the IPSV group (7.06±1.32 d) (p < 0.001). NIV reduced significantly the duration of ETI weaning failure, nosocomial pneumonia, ICU stay and hospital stay.

Conclusions: 1. NIV like IPSV significantly and similarly improves gas exchange during weaning, of patients with ACRF secondary to AECOPD, from invasive MV. 2. NIV reduces significantly the duration of ETI weaning failure, nosocomial pneumonia, ICU stay and hospital stay.

P3786 Leptin kinetics in patient with obesity hypoventilation syndrome (OHS) during non-invasive ventilation (NIV)
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Background: Leptin is pleiotropic hormone which has important physiological effects in patients with OHS. Currently there is no data about leptin kinetics for the management or follow-up of OHS patients with acute respiratory failure (ARF).

Objectives: To evaluate the leptin kinetics in patients with OHS during hypercapnic AHRF treated with NIV therapy.

Methods: Our prospective observational study included 19 OHS patients hospitalized for AHRF (age 55.9±12.2 yrs, BMI 56.7±8.3 kg/m², PaCO2 42.6±10.35 mmHg, PaO2 58.5±12.2 mmHg), all patients received NIV during hospitalization. Serum leptin levels, arterial blood gases, pulmonary function and echocardiography tests were measured.

Results: Initial leptin concentration was not significantly elevated in OHS patients (38.6±6.97 ng/ml), and after 10-14 days of NIV therapy leptin levels significantly decreased (to 32.1±12.5 ng/ml, p < 0.001). But in patients with more slower reduction of PaCO2 (n=9) leptin levels didn’t change significantly at hospital discharge.

Intentional leptin concentrations correlated with residual lung volume (r=0.76, p=0.04) and leptin kinetics correlated with change in PaCO2 (r=0.49, p=0.04) and change in PaO2 (r=0.75, p<0.001). Patients with slower leptin kinetics had higher BMI, more severe hypercapnia, less pH and left ventricular ejection fraction (p<0.05); they needed more intensive NIV and had an increased risk of hospital readmission during 3 months (n=28 0.004).

Conclusions: Assessment of leptin kinetics in OHS can help to predict outcome of NIV therapy and it may be of value for guiding NIV intensity in these patients.
with or without other pathology (6%) vs (4%), interstitial lung disease (55%), OHS (5.2%), kyphoscoliosis (17%), heart failure (16%) and neuromuscular disease (41%) When comparing epidemiological data, comorbidities, and side effects between the group died and those who survived after treatment, we founded significant differences in the deceased group older, less obese.

Conclusions: It is necessary to performance a detailed analysis of mortality in each group of pathology In COPD and OHS, which are the most ventilated, it is quite worthwhile to carry out NIV. The palliative patients group increase mortality rates so it is very important to analyze this group separately. To carry out NIV may be an alternative for patients who do not fulfill ICU admission criteria.

P3789
Decision making in acute hypercapnic respiratory failure due to COPD: Criteria in patient selection & determining ceiling of care
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Background: Non-invasive ventilation (NIV) is effective in acute hypercapnic respiratory failure (AHRF) due to COPD but the UK National COPD Audit (2008) raised concerns about patient selection; only 70% of eligible patients received NIV and invasive mechanical ventilation (IMV) was used in only 3% if NIV failed.

Aims: The aim of this study was to ascertain criteria clinicians use to make decisions regarding NIV.

Methods: A 12 point questionnaire was sent to doctors involved in acute care of patients admitted with acute exacerbation of COPD. Key areas included arterial blood gas (ABG) criteria, prognostic factors and decisions on ceiling of care. Comparisons were made between grades and specialities.

Results: 31 questionnaires were completed. 61.5% consultants, 16.1% specialist registrar (SPR), 24.5% other training grades (OT). Specialties: ITU 16.1%, Respiratory (RESP) 22.6%, Other general medical 61.5%. Most (74.1%) made decisions on NIV at least weekly. There was poor agreement on ABG criteria for NIV (<7.35). Adherence to guideline criteria for NIV varied by specialty. RESP 85.7% v non-RESP 41.6% OR 8.4 (1.08-59.8). Agreement on prognostic criteria was poor (K 0.17). 80% of SPR and 28.5% OT grades frequently make decisions on ceiling of care.

Conclusions: AHRF due to COPD is often managed by non-respiratory physicians. There is marked divergence from guideline criteria for initiation of NIV. There is poor agreement between physicians regarding prognostic criteria used to determine ceiling of care. These decisions are frequently made by junior medical staff.

P3790
Prognosis after non-invasive ventilation (NIV) for chronic obstructive pulmonary disease (COPD)
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Introduction: Non-invasive ventilation is now standard therapy for acute type 2 respiratory failure secondary to COPD. It reduces mortality, intubation rate and length of stay even when given in a general respiratory ward. Therefore, many patients who were considered to have othervise had not survived, are now successfully discharged.

Aims and objectives: To assess survival and remission rate over subsequent one year in these patients in “real life” while receiving routine medical care in the community.

Methods: Retrospective review of 50 randomly selected patients admitted between 12/2001 and 9/2009 to Blackpool Victoria Hospital, a large district general hospital in North West of England.

Results: MF: 37:13, mean age 68.9 years (SD= 10.9). 49/50 patients were current (n=19) or ex (n=30) smokers. 26/49 (53%) were on long term (n=11) or short burst (n=15) oxygen. 3 had been previously admitted to ITU and 9 had received NIV; 6 patients had pneumonia and 17 evidence of cor pulmonale on ECG at the time of admission. 26/50 (52%) made recovery with NIV in the ward despite pH of <7.20 (5/30 had pH of <7.0). 14/48 (29%) had died during subsequent one year (survival status unavailable=2). Readmission rate was 74% and 48% were admitted more than once (x1=13 pts, x2=8 pts, x3=4 pts, x4=4 pts, x5=6 pts, x6=1 pt, x7=1 pt). Conclusion: One third of patients who were discharged after receiving NIV for an exacerbation of COPD died in the subsequent year. Majority of these patients required readmission, many more than once. Further research is required to optimally treat this high risk group to improve quality of life and and reduce health care costs.


P3791
Outcome analysis of “do not resuscitate” versus “full resuscitation” patients with acute exacerbation of COPD treated with noninvasive ventilation in a pulmonary unit
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Introduction: Noninvasive ventilation (NIV) is common practice in acute respira-
tory failure due to acute exacerbation of COPD (AECOPD). NIV is administered to patients with both “Do Not Resuscitate” (DNR) and Full Resuscitation (FR) order. Little is known about the outcome of DNR-patients treated with NIV in a pulmonary unit, compared to patients with a FR order.

Methods: In a single centre study, during a period of three years, we followed all patients with AECOPD who underwent NIV in a pulmonary unit (n= 67). NIV was initiated in case of respiratory acidosis with pH<7.35, using a stepwise protocol. Resuscitation policy was established earlier in the outpatient clinic or in the emergency unit at presentation. The outcome was failure of treatment, which was defined as 1) in-hospital mortality, 2) mortality within three months after discharge and 3) transfer to the ICU (only in the FR-group). The results of the DNR-group (n=22) and the FR-group (n=45) were compared.

Results: In the DNR-group 9 patients died in the hospital and another 3 died within three months after discharge (total failure: 55%). In the FR-group 1 patient died in the hospital, no extra mortality was observed within three months after discharge and 11 patients were transferred to the ICU (total failure: 27%) (Fisher exact p = 0.05).

Conclusion: There was more failure of treatment in the DNR-group than in the FR-group. However, still a substantial number in the DNR-group benefited from NIV. To clarify in which DNR-patients NIV-should be performed, further research is warranted to identify parameters predicting outcome.

P3792
Patients’ perspective of acute non-invasive ventilation (NIV) for decompensated type 2 respiratory failure (T2RF)
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Background: A proportion of patients who receive NIV for decompensated T2RF subsequently become intolerant to it. Lack of patient understanding, inadequate medical supervision and/or explanation could potentially lead to poor patient compliance with NIV. We sought to explore patients’ experience and views on acute NIV.

Methods: A satisfaction questionnaire was completed by patients within 24 hours of receiving acute NIV on a respiratory ward.

Results: 115 patients (65 male, median age 68) completed the study. 83% patients received NIV for 2 or more days. Patient responses are shown in table 1. NIV was stopped due to intolerance in 26 cases (mask discomfort 14, claustrophobia 9 and nausea 3). Intention to have NIV in future was not affected by ventilator pressures applied, duration of ventilation, or whether or not the patient had previously had NIV.

Table 1

<table>
<thead>
<tr>
<th>Was the need for NIV adequately explained to you?</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 (64%)</td>
<td>31 (27%)</td>
<td>9 (10%)</td>
<td></td>
</tr>
<tr>
<td>Were you told what NIV involved?</td>
<td>30 (26%)</td>
<td>56 (49%)</td>
<td>29 (25%)</td>
</tr>
<tr>
<td>Were you told what treatment you would receive if NIV failed?</td>
<td>29 (25%)</td>
<td>76 (66%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Have you had NIV previously?</td>
<td>30 (26%)</td>
<td>85 (74%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Overall, were you satisfied with NIV?</td>
<td>64 (56%)</td>
<td>36 (31%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Would you have NIV again if needed?</td>
<td>79 (69%)</td>
<td>25 (22%)</td>
<td>11 (9%)</td>
</tr>
</tbody>
</table>

Conclusion: A significant proportion of patients found NIV unpleasant and would refuse such treatment in future. Our data also highlights a lack of understanding of NIV by many patients receiving this therapy. Our findings have significant implications for patient education in respiratory units, as well as choice of equipment using NIV, both of which may impact on patient acceptance of therapy, and mortality.

P3793
Pulmonary gas exchange during mechanical non invasive ventilation in acute hypercapnic patients with obesity hypventilation syndrome (OHS)
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Introduction: It is well known that non invasive ventilation in chronic respiratory diseases improves arterial blood gases by enhancing alveolar ventilation without relevant changes in ventilation-perfusion (VA/Q) relationships. (O.Duc et al., Am J Resp Crit Care 1997:150:1-6). The adequate patient-ventilator synchronism throughout the breathing cycle should be a priority to ensure appropriate alveolar ventilation.

Hypothesis: We hypothesize that Pressure Support Ventilation (PSV) may be a useful modality of non invasive ventilation in hypercapnic patients with a restrictive ventilatory defect due to Obesity Hypoventilation Syndrome (OHS).

Aims: To this end, the effects of PSV versus VSV (volume support ventilation) on pulmonary gas exchange were analyzed in twenty hospitalized patients with hypercapnic respiratory failure due to OHS (BMI: 39 ± 7mmHg). Blood Gases at the time of the study (Fio2 0.21): pH (7.34±0.03), PaCO2 55±10 mmHg, PaO2 62.5±3 mmHg, Al-aO2 21±5mmHg.

Methods: Pulmonary gas exchange were measured at 30’ in each of the conditions.

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Non-invasive ventilation in acute respiratory failure in a respiratory intensive unit care (RICU) – Characterization and predictors of failure

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Aims: The use of NIV has proliferated in the last decades in order to support patients with acute respiratory failure. We aimed to analyze NIV’s success in RICU.

Methods: A systematic retrospective review was performed of all hospitalized patients for NIV in our RICU, from February 1 to July 31, 2010.

Results: NIV was performed in 79 patients, 73% were male, with a mean age of 70 years (35-95). Reasons for NIV were acute respiratory failure in 66 patients and continuation of NIV resulting from step-down ICU in 13. Six patients had hypoxemia, 64 hypercapnia and 9 mixed acidosis. Most patients had chronic diseases (cardiac and respiratory), 62% had previous hospital admissions and 27% previous invasive mechanical ventilation. Infectious respiratory exacerbations were the main cause for admission. In 18 patients the intubation decision was made. Average stay in RICU was 10 days (1-76). The majority of the patients had favorable evolution under NIV (57), however there were 22 NIV failures, with 5 ICU transfers. Concerning the group of NIV failure, they were significantly older (p=0.02), showed more previous hospital admissions (p=0.03), more nosocomial respiratory infections (p=0.001), a lower PaO2/PaCO2 (p=0.015), more extensive radiological disease (p=0.017), more sepsis underling disease (p=0.031), more renal disease (p=0.009) and end-stage palliation (p=0.000).

Conclusion: NIV is a common and indispensable treatment in a ICU. NIV’s results are in accordance with the severity of underlying disease, acute exacerbations and with the use of NIV as ceiling support.
NIV is used in 75% of RW with high dependency unit (HDU) and in 27% without HDU. The main indication to NIV has been acute exacerbation of COPD, 73% of all patients treated with NIV. Majority of RW (71%) treat up to 5 patients per month.

Main obstacles to development of NIV is lack of equipment and adequate structure of the ward.

Conclusions: Prevalence of NIV availability within RW in Poland is low and strongly depends on the grade of hospital and the presence of HDU.

P3799
Can non invasive ventilation be effective without a dedicated service?
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Introduction: UK guidelines recommend that Non Invasive Ventilation (NIV) should be administered in a dedicated setting with specially trained staff [1]. Our institution is a large district general hospital serving a population of 330,000 in the North West of England. NIV is used on the admissions unit and respiratory wards. Despite very frequent use the service runs without recurrent funding, dedicated staff or educational program. The aim of our service evaluation was to establish whether our service is safe and effective.

Method: We retrospectively audited NIV treatment episodes between January - March 2009. If NIV was discontinued but restarted after 72 hours this was regarded as a new episode.

Results: We identified 45 NIV treatment episodes, averaging 21.8 patient-hours a day. Our patient group comprised 14 female and 25 male patients, with an mean age of 73.1 yrs (range 56-93 yrs). The mean duration was 45 hours (range 5-158). 27 (60%) were diagnosed as an exacerbation of COPD, 13 as pneumonia (29%) and 5 (11%) as cardiac pulmonary oedema. 25 episodes (56.6%) had no treatment plan documented in case of failure of NIV (56.6% COPD, and 56.6% of non COPD), 10 patients (22%) died (33.3% of COPD patients, 14.8% of non COPD) and 1 (2.2%) was referred to ICU.

Conclusion: Our mortality rate in COPD patients is comparable to a recent national audit [2]. However, there is evidence of less advance treatment planning and ICU referral.

References:

P3800
Directed differentiation of mouse embryonic stem cells into primordial lung progenitor cells
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Introduction: During normal development, a small population of foregut cells are specified into lung progenitors that give rise to the entire adult lung epithelium. The transcription factor Ttf-1(Nkx2.1) is the earliest marker of these progenitors. Little is known about the gene programs involved in lineage specification and differentiation of the lung progenitor cells.

Aim: To recapitulate early lung development in vitro and primordially lung cells, identified by Ttf-1 expression, to better understand lung development.

Methods: We developed a faithful lung epithelial reporter line with the GFP reporter gene targeted into the Ttf-1 locus of mouse E12.5 ES. These ESCs were differentiated into endodermal cells using Activin-A in serum-free media. To recapitulate anterior and ventral endodermal patterning we used a combination of growth factors and inhibitors. GFP-positive cells emerged after 9 days in culture. GFP-positive cells were sorted by FACS and analyzed by quantitative real-time PCR at various time points.

Results: Clusters of GFP+ cells were observed from day 9 onwards. These cells expressed the endodermal marker Foxa2 and did not express neurectodermal markers above baseline undifferentiated stem cells. With further culture and FGF2+TGFa stimulation, purified Ttf1-GFP+ cells were lung and thyroid competent as evidenced by upregulation of markers SPC, SPB, CC10, FoxJ1, & CFTR suggesting a lung-like phenotype, and Thyroglobulin, Pax8 & TSHR suggesting a thyroid-like phenotype.

Conclusion: Our in-vitro system yields a purified population of Ttf-1 positive endodermal cells of a molecular phenotype reminiscent of primordial lung and thyroid progenitors.

P3801
Developmental profile of cellular pathways regulating protein breakdown in the fetal and postnatal diaphragm
Yong Song, Jane Pinlow. School of Women's and Infants' Health, The University of Western Australia, Perth, WA, Australia

Studies on diaphragm weakness and atrophy focus on adult muscle, but the preterm diaphragm might be more susceptible to injury. Characterization of the ontogeny of protein degradation pathways responsible for muscle atrophy would help further understanding of the altered signaling pathways under pathologic conditions of preterm babies. Here, we performed the baseline study of major proteolytic path-ways and antioxidant capacity in lambs from 75 d to 200 d postconceptional age. The diaphragm tissues were collected and analysed for gene expression and/or protein abundance in a set of key pathway components in conjunction with proteolysis/antioxidant activity. Our results showed that calpain and caspase 3 in gene and protein expressions exhibited a similar profile with advancing gestation, increasing from 75 d to 100 d of 128 d and subsequently decreasing gradually toward full term. In contrast, ubiquitin conjugating and ligase genes did not change during gestation. All proteolytic genes examined (except Ubiquitin) were up-regulated rapidly after delivery, with a similar development and observed in protease activities. Unlike proteolytic pathway pattern, antioxidant gene expression demonstrated a steady increase from 75 d gestation until 24 h after birth, followed by a significant reduction at 7 w of postnatal age (p < 0.002). The proteolytic signaling and an-tioxidant capacity patterns reflected the adaptive process to metabolic change and muscle maturity with development. The data from this study may partly explain the susceptibility of preterm infants to respiratory failure in response to injurious ventilation and/or clinical stressors such as inflammation and hypoxia.

P3802
PECAM-1 single nucleotide polymorphisms and idiopathic pulmonary fibrosis
Michael Crooks, Ahmed Fahim, Simon Hart. Division of Cardiovascular and Respiratory Studies, Castle Hill Hospital, Hull, United Kingdom

Background: Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias and carries a prognosis worse than most cancers. However, the pathogenesis of this disease remains incompletely understood. Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1) is a 130 kDa glyco-protein that has been implicated in pulmonary fibrosis in a strain of knockout mice. We assess the prevalence of the PECA-1 single gene polymorphisms and the serum concentration of PECA-1 in IPF patients versus controls.

Methods: Samples of full blood were collected from 37 patients with IPF and 41 controls. DNA was extracted from whole blood using QIAmp DNA Blood Midi Kit (Qiagen, Valencia, CA). PCR was performed using primers specific to exon 3, exon 8 and exon 12 of the PECA-1 gene. Purified PCR products were sent toEurofins MWG Operon for sequencing. The serum concentration of soluble PECA-1 was assessed using ELISA.

Results and discussion: No significant difference was observed in the prevalence of single gene polymorphisms in exon 3, 8 or 12 of the PECA-1 gene. The PECA-1 concentration was significantly higher in the IPF group versus controls (106.177ng/ml vs 84.327ng/ml respectively, p=0.0398) with elevated sPECA-1 concentrations associated with better lung function (p=0.038).

Conclusions: There was no significant difference in the prevalence of single gene polymor-phisms in the PECA-1 gene was observed between IPF and control groups. Serum PECA-1 concentration was elevated in IPF patients versus controls how-ever it is not possible to determine whether this is important in the pathogenesis of the disease or a secondary event resulting from cell injury and aberrant tissue repair.

P3803
Up-regulation of collagen type V mRNA in a model of systemic sclerosis
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Background: We have described an animal model of systemic sclerosis (SSc) induced by type V collagen (COLV) that resembles the human disease. The aim of this study was to investigate the early disease in the lungs of this model with special emphasis on collagen deposition and mRNA collagen synthesis.

Methods: Female rabbits from New Zealand lineage were immunized with COLV plus Freund’s adjuvant (FA). Animals immunized only with FA were used as controls. The animals were sacrificed at day 7, day 75 and day 210 and the lungs submitted to immunofluorescence, real-time qPCR and biochemical examination. Results: The immunolabeling for the COL I, III and V by immunofluorescence showed an intense expression of COLV in the bronchovascular interstitium near the inflammatory infiltrate of COLV-rabbits at day-210. Additionally, morphologic analysis demonstrated that the progressive remodeling of the extracellular matrix observed in this group of animals was characterized by thickened COLV deposition with distorted fibrils. In accordance with these observations, the real-time qPCR revealed markedly up-regulation of COLV mRNA of the COLV-group at day-210 comparing with controls (p<0.001). The content of hydroxyproline was compared for COLV-group and controls at day-7, day-75 and day-210, suggesting that the day-210 group represents an early disease without established fibrosis.
Interstitial Lung Disease Unit, Athol Wells, Elizabeth Renzoni, Gisela Lindahl.

Identification of stable housekeeping genes for real-time PCR in human of commonly used HKGs; resected tumors, n=10) lung tissue was used to assess variation in expression

Background: Quantitative real time PCR is an important tool in investigating gene expression levels in human lung fibroblasts under the conditions tested, and show further in geNorm all had an expression stability of M<0.70).

Methods: Serum-deprived MRC5 cells (human fetal lung fibroblast cell line) were pre-incubated with synthetic LXR agonist T0901317 and natural agonist 22(R)-hydroxysterol, and were differentiated into myofibroblasts by TGF-β1 for 48 hours. Changes in u- smooth muscle actin (α-SMA) and phosphorylated-Smad2/3 were analyzed by western blot. The inhibitory effects of irreversible PPARγ antagonist GW-9662 on anti-fibrotic abilities of LXR agonists were also examined.

Results: LXR agonist T0901317 and 22(R)-hydroxysterol inhibited TGF-β1 driven myofibroblast-differentiation as determined by α-SMA by western blot. T0901317 did not inhibit Smad2/3 phosphorylation. An irreversible PPARγ antagonist GW-9662 did not reverse the inhibition of myofibroblast-differentiation by T0901317.

Conclusion: LXR agonists have novel and potent anti-fibrotic effects in human lung fibroblasts.

P3084 Anti-fibrotic effects of liver X receptor agonists in human fetal lung fibroblasts
Shu Hayata, Shigeki Chiba, Takafumi Ito, Masahito Ebina, Toshihiro Nukiwa Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Introduction: Idiopathic pulmonary fibrosis is a progressive life-threatening disease for which anti-inflammatory agents such as glucocorticoids have no therapeutic effect. Liver X receptors (LXRs), which are nuclear receptors activated by oxysterols as natural ligands, show similar tissue distribution patterns with glucocorticoid receptor and peroxisome proliferator-activated receptor (PPARα,γ). LXRs play important roles not only in cholesterol metabolism and triglyceride synthesis, but also in inflammation and innate immunity. Previous studies showed anti-fibrotic effects of PPARγ agonists, but it remains unknown whether LXRs agonists have anti-fibrotic abilities.

Aims: The aim of our current study is to analyze anti-fibrotic effects of LXR agonists on human lung fibroblast.

Methods: Serum-deprived MRC5 cells (human fetal lung fibroblast cell line) were pre-incubated with synthetic LXR agonist T0901317 and natural agonist 22(R)-hydroxysterol, and were differentiated into myofibroblasts by TGF-β1 for 48 hours. Changes in u-smooth muscle actin (α-SMA) and phosphorylated-Smad2/3 were analyzed by western blot. The inhibitory effects of irreversible PPARγ antagonist GW-9662 on anti-fibrotic abilities of LXR agonists were also examined.

Results: LXR agonist T0901317 and 22(R)-hydroxysterol inhibited TGF-β1-driven myofibroblast-differentiation as determined by α-SMA by western blot. T0901317 did not inhibit Smad2/3 phosphorylation. An irreversible PPARγ antagonist GW-9662 did not reverse the inhibition of myofibroblast-differentiation by T0901317.

Conclusion: LXR agonists have novel and potent anti-fibrotic effects in human lung fibroblasts.

P3085 Identification of stable housekeeping genes for real-time PCR in human pulmonary fibroblasts
Caroline Stock, Patricia Leoni, Xu Shi-Wen, David Abraham, Andrew Nicholson, Athol Wells, Elizabeth Renzoni, Gisela Lindahl. Interstitial Lung Disease Unit, Royal Brompton Hospital, London, United Kingdom Dept Histopathology, Royal Free Hospital, London, United Kingdom Dept Histopathology, Royal Brompton Hospital, London, United Kingdom

Background: Quantitative real time PCR is an important tool in investigating gene transcription levels under different biological conditions. Accurate results rely on controlling for differences in mRNA quantity and quality between samples, controlling for differences in mRNA quantity and quality between samples, which are commonly achieved by normalisation to expression of housekeeping genes (HKGs). Expression levels of the HKGs used is critical, but to date no systematic study controlling for differences in mRNA quantity and quality between samples, com-

Methods: Microarray data of gene expression in explanted fibroblasts from SSC-ILD (systemic sclerosis lung biopsies, n=8) and control (normal periphery of resected tumors, n=10) lung tissue was used to assess variation in expression of commonly used HKGs: ACTB, GAPDH, HPRT1, RPL32, TBP, and YWHAZ (HUGO nomenclature). The four most stable genes (<15% variability) were selected by qRT-PCR in an independent experiment in which SSC-ILD (n=3) and control (n=3) fibroblasts were cultured in 0.1% BSA for 24hrs, and a further 24hrs with or without IFNγ (10ng/ml). A measure of expression stability (M), the average pairwise variation with each of the other studied genes (with a recommended maximum value of 1.5) for each HKG, was calculated using the program geNorm (Vandesompele, J. et al. Genome Biology 2002;3:4-3.12).

Results: While ACTB and GAPDH were relatively unstable, the four HKGs tested further in geNorm all had an expression stability of M<1.0; the most stable gene was YWHAZ (M=0.56), followed by HPRT1 (M=0.60), RPL32 (M=0.67), and TBP (M=0.70).

Conclusion: We have identified four HKGs suitable for normalisation of mRNA expression levels in human lung fibroblasts under the conditions tested, and show the necessity for empirical identification of HKGs.

P3086 Molecular screening – A search for potential drugs for idiopathic pulmonary fibrosis
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Background: Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease with a poor prognosis and very few therapeutic options. On a molecular level, patients with IPF have increased amounts of BMP inhibitor gremlin in their lungs (BMP, bone morphogenetic protein). Gremlin decreases BMP signalling and, as a consequence, TGF-β signalling is increased (TGF-β, transforming growth factor-beta). The balance between BMP and TGF-β signalling activities in the lung is of crucial importance during e.g. regenerative processes. Thus, severe alterations in these signalling activities are likely to contribute to the pathogenesis of IPF.

Aim: To use high-throughput chemical screening as an approach to find molecules which could normalize the TGF-β/BMP balance in the fibrotic lung.

Methods: The screen was performed with a commercial chemical library with ca. 2000 compounds. The set-up is based on two reporter cell lines that contain either a BMP- or a TGF-β-responsive element linked to a luciferase gene. The effect of the chemicals is evaluated by measuring the changes in the expression of the luciferase gene.

Results: Using this approach we have been able to identify compounds which modulate the BMP/TGF-β signalling balance in the reporter cell lines. One compound was also shown to modulate endogenous BMP/TGF-β signalling activities in lung epithelial cells.

Conclusions & future directions: Using chemical compound screening it is possible to identify small-molecular weight compounds that modulate gene expression in lung epithelial cells. These compounds are potential drugs for the prevention of progression of IPF. Their effects will be evaluated in preclinical in vivo studies using a mouse model of pulmonary fibrosis.
concentration was measured by turbidimetry and PI-photon type identified by iso-electrofocusing. The PI*P and PI*V alleles were confirmed by real-time PCR: rare phenotypes were identified by sequencing.

Results: 53 (12.6%) lung disease patients and 18 (6.4%) liver disease patients demonstrated AAT deficiency phenotypes. Calculated frequencies expressed per 1000 were for PI*Z 46.6 (95% CI: 32.3-60.8), PI*P 20.3 (95% CI: 10.8-29.8) in regards to lung disease, and 19.6 (95% CI: 3.1-36.0) for liver disease patients. The AAT gene prevalence calculated by Hardy-Weinberg equilibrium were: 1/16 for MM, 1/26 for MS, 1/24 for SS for MM, 1/11 for MZ, 1/30 for SZ and 1/462 for ZZ in liver disease patients.

Conclusion: Our results show relatively high frequency of AAT deficiency among Polish patients with chronic obstructive respiratory disorders. Estimated frequency for PI*Z and PI*P allele in respiratory group was about two-fold higher than in liver disease patients and four-fold higher than estimated prevalence in healthy Polish population.

P3809 Proteomic analysis of antioxidant proteins in bronchoalveolar lavage of patients with pulmonary Langerhans-cell histiocytosis
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Pulmonary Langerhans-cell histiocytosis (PLCH) is a tobacco smoke-related diffuse lung disease of unknown etiopathogenesis. Oxidative-mediated lung injury has been documented in patients with PLCH. In this study we analyzed by 2-dimensional electrophoresis, BAL protein expression of antioxidant proteins in a group of patients with PLCH, a group of healthy smokers and a group of no-smoker controls in order to better understand the potential role of oxidant/antioxidant balance in the disease pathogenesis. Among the differentially expressed spots identified by us, the proteins implicated in the antioxidant defense where thioredoxin (THHO), ALBU, ceruloplasmin (CERU) and glutathione peroxidase 3 (GPX3). THIO was a protein identified from a spot down-regulated in PLCH versus smoker controls (p<0.01). It plays a protective role against cigarette smoke-induced lung oxidative damage and against Th2-driven airway inflammation. CERU isomor 1 and 2 were significantly upregulated in PLCH patients compared to no-smoker controls (p<0.01) while CERU isomor 3 was upregulated in patients than smoker controls (p<0.05). GPX3 was absent in 2/2-gels of patients with PLCH and it was significantly over-expressed in smokers than no-smoker controls. In conclusion antioxidant defense could be involved in PLCH pathogenesis being the expression of antioxidant proteins significantly different in BAL of patients with respect to smoker or no smoker controls.

P3810 Endothelin-1 (ET-1) is a useful biomarker for early detection of ventilator-associated pneumonia (VAP) in mechanical ventilation children
Dymtria Smyrniote, Katerina Dmytrytseva, Oleksandra Nazarchuk, Anatoliy Staradub, Oleksander Mazulov, Konstantin Dmytrytsevan

Objectives: VAP is a severe complication limiting survival children. ET-1 is a peptide produced by pulmonary vascular endothelial cells that play a role in the pathophysiology of lung dysfunction. Whether ET-1 could predict VAP development is unknown.

Methods: Transbronchial biopsy specimens and serum and bronchoalveolar lavage were obtained from 23 children with VAP and 24 without VAP. The serum and bronchoalveolar lavage ET-1 concentrations were measured by enzyme-linked immunosorbent assay, and the ET-1 mRNA expression in the transbronchial biopsy specimens was examined using real-time polymerase chain reaction.

Results: ET-1 serum concentrations were greater in the patients with VAP (P<0.02); and ET-1 mRNA was significantly in the lung of those versus those without VAP at 3 and 12 day after start mechanical ventilation (P<0.01). At 3 and 12 days after start mechanical ventilation, the ET-1 concentrations were significantly elevated in the serum (P<0.01 and P<0.001, respectively) and bronchoalveolar lavage (P<0.01 and P<0.01, respectively) of children with compared with those without VAP. On logistic regression analysis, 3-day after start mechanical ventilation serum ET-1 level predicted for VAP (odds ratio, 1.01; 95% confidence interval, 1.003-1.027; P<0.07; odds ratio, 2.8; 95.3%, confidence interval, 1.01 - 8.4; P< 0.001). The serum ET-1 level at 12 days was diagnostic for VAP (odds ratio, 4.1, 95% confidence interval, 1.4 - 11.3; P=0.009).

Conclusions: Elevated serum ET-1 concentrations were predictive of VAP, and the assessment of circulating ET-1 might be beneficial in diagnosing and monitoring VAP.

Circulating lymphocytes are increasingly used as a surrogate cell type to reflect changes in ADRβ2 density elsewhere in the body, particularly the respiratory system. However, ADRβ2 density is non-uniform among lymphocyte subsets and potentially varies between individuals.

Aim: To assess the extent of variability in ADRβ2 density on human peripheral blood mononuclear cells (PBMC) including lymphocytes and monocytes.

Method: PBMC were isolated from 10 healthy subjects by density gradient centrifugation with Ficoll-Paque. Cell surface & total ADRβ2 of lymphocytes (CD4+), monocytes (CD3+), and lymphocytes (CD14+) were measured using FACS. Geometric mean fluorescence (GMF) was used as the indices for ADRβ2 density per cell.

Result: Surface ADRβ2 - GMF increased by 3.34 and 4.62 folds over negative controls for lymphocytes and monocytes respectively (P=0.16). However, distribution of GMF between samples suggests greater variability in ADRβ2 density in lymphocytes vs monocytes (P<0.06). Proportion of ADRβ2-positive cells was higher in monocytes vs lymphocytes (71.9% vs 36.7%, p<0.02). Total ADRβ2 - GMF increased by 12.4 and 9.61 folds for lymphocytes and monocytes respectively (p<0.05). Proportion of ADRβ2-positive cells were similar between samples of lymphocytes 80% vs 85%, but monocytes 86% vs 85% but greater variability was observed for lymphocytes (range 27.9%-99%) vs monocytes (range 66%-100%).

Conclusions: Despite similarities in surface and total ADRβ2 density, lymphocytes display greater inter-subject variability compared with monocytes. This has implications in experimental designs & interpretation of changes in ADRβ2 density in studies using human PBMC as an alternative to primary cells from organ of interest.

P3812 Apocynin augments IL-6, IL-8 and TNF expression in A549 cells
Ioanna Stefanis, Milena Sokolowska, Rafał Pawlicki. Department of Immunopathology, Medical University of Lodz, Lodz, Poland

Reactive oxygen species (ROS) play an important role in many pathways and processes. An enzyme responsible for ROS production - NADPH oxidase represents an attractive therapeutic target. Apocynin is a small molecule that reversibly blocks NADPH oxidase activation and therefore inhibits ROS formation. Apocynin, in our previous studies, reduced some ROS concentrations in exhaled breath condensate of asthmatics, COPD patients, and healthy subjects. Therefore we decided to investigate apocynin influence on expression of IL-6, IL-8 and TNF in vitro. A549 cells were incubated with apocynin in concentrations: 0.25, 0.5, 1, 2 and 3 mg/ml. After 1h, 2h and 4h of incubation with each concentration RNA was isolated and reverse transcription was made. mRNA expression was assessed using real-time PCR.

Response-analysis revealed apocynin most effective influence after 2 and 4 hours of incubation. It caused increased expression of IL-6 (expression level (RQ) 0.64 – 2h and 0.62 – 4h vs 0.007 – base), and IL-8 (RQ 25.18 – 2h and 25.12 – 4h vs. 1.74 – base) in A549. Moreover, apocynin caused TNF expression increase in A549 after one and four hours of incubation (RQ 0.037 – 1h and 0.036 – 4h vs. 0.017 – base). Dose-response analysis showed apocynin to be most effective in concentration of 0.5 mg/ml. This dose caused increase of IL-6 expression (RQ 2 - control sample (CS) and IL-8 expression (RQ 101 vs 2 – CS, but also 1 mg/ml – RQ 30 vs 2 - CS). TNF expression was increased in samples incubated with 0.25 mg/ml (RQ 0.037 vs 0.02 – CS).

These findings may provide a novel therapeutic strategy and might be of importance in relation to inflammatory diseases.

P3813 Comparison the frequency of human T-lymphocyte type 1 (HTLV 1) infection in tuberculosis patients with control group without tuberculosis
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Introduction: Regarding to recognize the predisposing factors in Tuberculosis infection which is common in Khorasan, Northeastern province of IRAN this study investigate whether Humant-T-lymphocyte type 1 (HTLV 1) as an immunosuppressive factor increase the risk of tuberculosis.

Methods: A case控制 study was conducted on 278 pulmonary and extrapulmonary tuberculosis during 2007-2010, in city of mashad, capital of khorasan.Tuberculosis has been documented by goldstandard tests like spu-tumculture, BAL culture or cytology.For detection of HTLV1 antibody, ELISA method and as a confirming test western blot were performed. Healthy sex and age matched control group were 276 persons.
There is a acute problem with diagnostics of mycobacterios in Russia. Species identification of mycobacterial cultures is not performed in bacteriology labs. over Russia. There are no any statistical data for the incidence of NTM. Detection. We aimed to evaluate the level of NTM detection at examination of cultures from BACTEC MGIT 960 (BD, USA) in the course of 2010. 1520 positive MGIT tubes (obtained in 2010) were studied. Primary screening of cultures was performed using standard microbiological techniques blood agar culture and Ziehl-Neelsen stain. In addition real-time PCR I6E110 was done for all 1520 cultures. For suspected samples species identification was done using GenoTypeCM/AS (HAIN Lifescience, Germany) were carried out. Of 1520 cultures, 75 cultures (4.5%) belonged to NTM. Using GenoTypeCM/AS/ we performed species identification for 72 strains from 75. Following spectra of NTM strains were detected: M. fortuitum (15 strains), M. peregrinum (2 strains), M. chelonae (5 strains), M. abscessus (6 strains), M. xenopi (3 strains), M. gordonae (5 strains), M. smegmatis (7 strains), M. fortuitum (4 strains), M. kansasi (9 strains), M. avium (13 strains), M. intracellulare (3 strains). One of 3 detected by Hain test-system as a Mycobacterium spp. strain belonged to M. nonchormoenginem in accordance to sequence of 16S rRNA. Data allowed to conclude that 4.9% of 1520 cultures obtained from BACTEC MGIT 960 were NTM. Usage of exact and rapid molecular-genetic method - GenoTypeCM/AS helps to perform accuracy species identification of NTM. It helps physicians to ensure accurate diagnosis and prescribe adequate treatment.

P3814 Application of GenoTypeCM and GenoTypeAS to species identification of nontuberculous mycobacteria as a routine method in microbiology lab of CTLR, Moscow.

Tatiana Smirnova, Alena Vorobyeva, Elena Larionova, Sofia Andreevskaya, Larisa Cheremushkova. Microbiology Dep., Central TB Research Institute of RAMS, Moscow, Russian Federation.

We assessed the concentration of IL-2, IL-4, IL-10, IL-12 and TNF-alpha in supernatant in spontaneous and IL-2-, IL-4- and TNF-alpha-induced apoptosis. The quantity of com-mitochondrial cytochrome c in serum was also determined. The molecular mechanisms of lymphocyte apoptosis disregulation at Th1- and Th2- cytokine disbalance.

Elena Sazonova1, Olga Chechina 1, Oksana Zhukova2, Natalia Ruazanceva 1.
1Fundamental Medical University, Trinity State University, Tomsk, Russian Federation; 2Bacteriology and Physiotherapy, Research Institute of Bactanology and Physiotherapy of Federal MedicalObijective Agency, Tomsk, Russian Federation.

Much of the literature evaluates the Th1/Th2 balance concept to the level of paradigm. Although Th1 and Th2 cells are now virtually22 23 24 25 also involved in the presentation of many antigens, Th1 polarized cells play a major role in antiviral responses and Th2 cells are involved in antibody production. The Th1/Th2 paradigm is of particular interest for the development of immune-therapy.

The molecular mechanisms of lymphocyte apoptosis disregulation at Th1- and Th2- cytokine disbalance.

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P3815 The molecular mechanisms of lymphocyte apoptosis disregulation at Th1- and Th2- cytokine disbalance.

Elena Sazonova1, Olga Chechina 1, Oksana Zhukova2, Natalia Ruazanceva 1.
1Fundamental Medical University, Trinity State University, Tomsk, Russian Federation; 2Bacteriology and Physiotherapy, Research Institute of Bactanology and Physiotherapy of Federal MedicalObijective Agency, Tomsk, Russian Federation.

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P3816 Diverse effects of PAI-1 proteins on lung and prostate cancer cell invasion.

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Acquisition of ability to uncontrolled migration is one of the fundamental properties of cancer cells, enabling them to infiltrate tissues and metastasize PAI-1 is the major physiological inhibitor of urokinase (uPA), which plays a key role in migration and invasion of tumor cells. The aim of present study was to analyze the impact of increasing concentrations of PAI-1 mutated forms. VLHL PAI-1 with very long half-life time, Vn PAI-1 devoid of affinity towards vitronectin and wPAI-1 on lung (A549, H1299) and prostate (LNCaP, DU145) cancer cells invasive activity. Selected cell lines are characterized by different (normal and high) urokinase production. No effect of PAI-1 proteins on invasiveness of lung cancer cells was observed, while dose-dependent significant inhibition was demonstrated in both prostate cancer lines (DU145 and LNCaP) cultured with VLHL PAI-1 (respectively p<0.05 and p<0.01) and Vn PAI-1 (p<0.05). Not surprisingly wPAI-1 significantly stimulated prostate cancer cells invasiveness in all concentrations. PAI-1 inhibitory effect on prostate cancer invasive activity is associated with anti-proteinase activity. Lung cancer cells invasive regulation seems not to be PAI-1-urokinase regulated.

P3817 Role of bronchoscopy in lung cancer translational research: Tumor harvest for the lung cancer mutation consortium (LCMC) studies.

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Introduction: The LCMC is a multi-institution collaboration to collect 1,000 cases of advanced (stage IIIIB/IV) Adenocarcinoma for rapid analysis of multiple genes and conduct important in LC pathway, to accelerate biomarker validation & discovery, to develop novel therapeutics.

Aim: To address the need to harvest sufficient tumor from subjects who are often not suitable surgical candidates. To advance bronchoscopic harvest of tumor sufficient for multigene studies.

Method: 68 lung Adenocarcinoma pts consented (3-10 and 2-11) for sending tumor tissue to Utah Colorado for multiple molecular analysis FISH analysis for MET amplication & ALK protein fusion, gene mutations by SNaPshot testing. APC, AKT1, BRACFN1NB1, EGFR, FLRT, JAK2, KIT, KRAS, MAPK1, NOTCH1, NRAS, PIK3CA, PTEN, TP53. One pathologist (P1) review slides for tumor cellularity and adequacy for 20 extra studies.

Results: 2 subjects ineligible (AC non-awarded), 15 QNS, 33 with tissue successfully sent, 18 awaiting review of slides. Material deemed insufficient 4 - effusion cell block, 2 excised nodes, 9 bronch samples but 3/9 had sufficient tissue for sufficient sample testing KRAS, EGFR, ALK, hence likely exhausted. Of 33 successful send-out: 17 lung surgery, 5 brain mets, 2 pleural metast biopsies, 2 CT core bx. 7/53 (21%) from bronchs: 3 endo & 2 each transbronchial forceps.

Conclusion: Of 16 bronch specimens evaluated for multiplex tumor pathway testing after local site clinical testing, 7 (44%) adequate, 6 (37%) QNS, 3 (19%) likely exhausted.

P3818 GSTT1 and CYP1A polymorphisms, tobacco smoking and lung cancer in northern India.

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Background: Susceptibility to lung cancer has been shown to be modulated by inheritance of polymorphic genes encoding cytochrome P450 1A1 (CYP1A1) and glutathione S transferases (GSTT1), which are involved in the bioactivation and detoxification of environmental toxins.

Aim: To investigate the role of GSTT1 and CYP1A polymorphism in the susceptibility to lung cancer patients in northern India.

Methodology: We have recruited 456 study subjects, 218 cases of lung cancer and 238 healthy controls were recruited from northern India. Genetic polymorphism screening of GSTT1 and CYP1A1 was conducted by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP).

Results: The frequencies of GSTT1 Null, alleles were significantly differ between patients and controls, with odds ratio (OR) =0.52; 95% confidence interval [CI] = 0.35-0.79, p<0.002, but -6235 T-C genotype were not associated with lung cancer patients with healthy controls. GSTT1 null genotype were significant associated.
with the smoker lung cancer patients, with odds ratio [OR] = 1.76; 95% [CI] = 1.17-2.66; p= 0.007.

Conclusion: In this northern Indian population, 86.7% of male and 13.3% of female lung cancer incidence were explained by tobacco smoking. Deleterious polymorphisms of the GSTT1 had an effect on the risk of lung cancer.

P3819 Comparing LYVE-1 and D2-40 expression in small cell lung carcinomas (SCLC): association with clinical parameters and lymphatic invasion

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Introduction: Lymphangiogenesis is actively facilitating tumor metastasis. LYVE-1 and D2-40 are two new lymphatic endothelial markers; their expression and prognostic impact in SCLC still remain vague.

Aim: To investigate the lymphangiogenic expression in SCLC we measured the intratumoral lymphatic microvessel density (ILMVD), the lymphatic invasion (LI) and their correlation with clinical parameters.

Materials and methods: Retrospective study of 55 SCLC patients (mean age: 68.1 years, range 40-89). Histological specimens from all patients were immunohistochemically stained for D2-40 (epitope of podoplanin) and LYVE-1 (CD44 homolog). Calculation of ILMVD and assessment of LI were performed and correlation with clinical data followed.

Results: D2-40 and LYVE-1 were expressed in all specimens whilst LI in 59.6%. D2-40 and LYVE-1 ILMVD were associated with the stage at diagnosis (p=0.017 and p=0.03 respectively) and LI (p=0.00 and p=0.02 respectively). D2-40 ILMVD was particularly associated with certain target organs for metastasis (liver p=0.001, adrenal p=0.014, brain p=0.007). LI was associated with stage (p=0.05) and all target organs for metastasis (p<0.05). ILMVD D2-40 and LYVE-1 weren’t associated with LI and survival.

Conclusions: D2-40 and LYVE-1 and LI were highly expressed in SCLC and independently associated with poor patient outcome, thus presenting new insights in prognosis. D2-40 presented a more potent role by associated with certain target organs for metastases. Defining subgroups of patients with poorer prognosis at the time of diagnosis could reinforce the development and application of new targeted therapeutic strategies.

406. COPD: clinical studies and animal cell models

P3820 Altered composition of airway basement membranes in COPD

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Rationale: The basement membrane provides a chemical and mechanical structure which is crucial for the mucosal homeostasis in the airways. Thickening of lamina reticularis is a common feature in asthma but the situation in COPD is less clear. Our hypothesis was that there are quantitative and qualitative alterations in airway basement membranes in COPD that influence the integrity of epithelial and mesenchymal cells.

Methods: Lung tissue sections from COPD patients and control subjects were subjected to H & E and picrosirus-RED staining. Sections were also immunostained using antibodies against the small proteoglycans: decorin and biglycan. Fibroblasts were isolated from lung explants from COPD patients (n=8) (GOLD stage IV) and from control subjects (n=9) and proteoglycan production was examined in vitro.

Results: Using immunostaining showed an unevenly distributed thickening of lamina reticularis in bronchial and bronchiolar airways from COPD patients but not from control subjects. The thickened areas stained positive for picrosirus RED, which shows the presence of fibrillar collagens (collagen I and III). This was accompanied with increased immune-positivity for the small leucin-rich proteoglycans decorin and biglycan. Fibroblasts isolated from bronchial specimen from COPD patients had decreased production of the basement membrane stabilizing proteoglycan perlecain (p<0.05).

Conclusions: This data indicate that there are qualitative and quantitative alter-
The lungs may be involved in the pathogenesis of COPD. Interestingly, serum levels of sIL-18Ra in COPD (n=100) were significantly (P<0.001) lower than seen in non-smokers (n=51). Overexpression of IL-18Ra proteins in the lungs of COPD patients (with GOLD stage I [n=28], II [n=34], III [n=22], and IV [n=16]), 36 smokers and 51 non-smokers nor non-smokers. Interestingly, serum levels of sIL-18Ra in COPD (n=100) were significantly (P<0.001) lower than seen in non-smokers (n=51). Overexpression of IL-18Ra proteins in the lungs of COPD patients (with GOLD stage I [n=28], II [n=34], III [n=22], and IV [n=16]), 36 smokers and 51 non-smokers (n=51). Overexpression of IL-18Ra proteins in the lungs may involve in the pathogenesis of COPD.

P3824
Expression profiling of Th17 associated molecules in bronchoalveolar cells from patients with chronic obstructive pulmonary disease (COPD)
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Recently, the presence of inflammatory cells expressing IL-17A has been reported in the small airway subepithelium obtained from COPD patients (Eitacek A et al. Chest. 2010) which, with further evidence (reviewed in Alcorn JF et al. Ann Rev Physiol, 2010), suggests that Th17 immune response may participate in COPD pathomechanisms. However, to date there has been no data about the presence of IL-17A in human serum. We also found that serum levels of the complex Apocynin reduces H2O2 and NO- concentrations in exhaled breath condensate of COPD patients. It is well known that COPD is a preventable and treatable disease, characterized by not fully reversible airflow limitation. In individuals with COPD, there is a marked exacerbation of the inflammatory response, which increases with the progression of the disease. The molecular mechanism of exacerbations remains unknown; however, prolonged oxidative stress has been reported as potentially responsible for the exacerbation. Apocynin is an agent that inhibits activation of an enzyme responsible for ROS generation and thus – probably, alleviate inflammatory process. Therefore, we investigated the effect of nebulized apocynin in fourteen COPD patients in placebo-controlled, cross-over design study. Exhaled breath condensate was collected in three timespots (30, 60 and 120 min) after apocynin/placebo administration. The mechanism of apocynin was investigated. Moreover, safety parameters have been controlled throughout the study. Apocynin reduced hydrogen peroxide concentration in exhaled breath condensate 60 and 120 minutes after apocynin nebulization compared to placebo (0.43 μM ± 0.09 μM vs. 1.45 μM, p<0.05). No influence of apocynin on safety parameters, and no adverse effects has been observed. Our findings suggest that apocynin might be a promising agent to soothe locally inflammatory process and improve life quality of patients suffering from COPD.

P3827
Apolipoprotein E polymorphism and smoking in relation to cardiovascular disease - a case-control study
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Purpose: To evaluate the influence of ApoE genotypes on the risk of cardiovascular disease (CVD) and the interaction between ApoE and smoking in the Italian population. Methods: A total of 692 case patients and 719 control subjects, who underwent a complete clinical evaluation including a thorough medical history, physical examination, laboratory tests, ECG, and echocardiogram, were randomly selected from the records of the local hospital. The cases were divided into groups according to their ApoE genotype (E2, E3, and E4). The controls were randomly selected from the general population of the same age and sex. The influence of the ApoE genotypes on the prevalence of CVD was analyzed. Results: There was a significant difference in the prevalence of CVD between the genotype groups (p<0.05). The frequency of E4 allele was higher in the case group than in the control group (p<0.05). The prevalence of CVD was significantly higher in carriers of the E4 allele than in non-carriers (p<0.05). The interaction between the ApoE genotype and smoking was not significant (p>0.05). Conclusion: The ApoE genotype is associated with the risk of cardiovascular disease, and the interaction between ApoE and smoking is not significant. These findings suggest that the ApoE genotype may be a risk factor for cardiovascular disease in the Italian population. However, further studies are needed to confirm these findings and to elucidate the mechanisms involved.
Cigarette smoke exposure in mice leads to a loss of reversible cysteine oxidations PSSG and PSNO in lung
Cigarette smoke exposure in mice leads to a loss of reversible cysteine oxidations PSSG and PSNO in lung tissue. It is established that cigarette smoke causes irreversible oxidations in lung tissue. However, its impact on reversible and physiologically relevant redox-dependent protein modifications remains to be investigated. In this study the effect of cigarette smoke exposure in vivo was investigated on the covalent binding of glutathione to protein thiols, known as S-glutathionylation (PSSG), which can be reversed by the enzyme glutaredoxin 1 (Grx1). Also, protein S-nitrosylation (PSNO) which is the modification of protein thiols by NO and which is reversed by the enzyme ADH5 was investigated.

Both PSSG and PSNO levels in lung tissue were markedly attenuated after four weeks of cigarette smoke exposure in mice. This coincided with an attenuation of protein free thiol levels and an increase in protein carbonyl levels. Grx1 mRNA expression and activity were attenuated as well, whereas no alterations in expression or activity of ADH5 were observed. Taken together, cigarette smoke exposure decreases reversible cysteine oxidations PSSG and PSNO, which does not result in an increase in free thiols. These alterations are likely not the result of differences in regulatory enzymes, but of oxidative stress.

Hypoxic exposure after smoke cessation restores alveolar surface area in mice
Chronic obstructive pulmonary disease (COPD), which mainly results from chronic exposure to tobacco smoke, is a major public health burden with an effective treatment. We have previously shown that hypoxia can induce lung growth in adult mice [1]. The aim of this study is to investigate if sustained hypoxia can restore the loss of alveolar surface area caused by tobacco smoke.

Methods: We exposed C57BL/6J mice to 6 months of tobacco smoke (250 mg/m3 suspended particles in 2.5 h/day) followed by 3 months of sustained hypoxia (SH) with an FiO2 of 10% and appropriate control groups (no smoke/noxygenosis (N)). Pulmonary function was measured in anesthetized mice. Following euthanasia lungs were processed for morphometry, mean airspace chord length (Lm) was measured and alveolar surface area was calculated.

Results: Mice exposed to tobacco smoke had a trend towards a lower alveolar surface area compared to control mice even 3 months after smoke cessation (p = 0.10). SH increased total lung capacity, whereas Lm was unchanged. SH significantly increased the alveolar surface area in mice previously exposed to smoke (p = 0.008, Fig. 1), but not in control mice.

Conclusions: Sustained hypoxia after cessation of tobacco smoking restores alveolar surface area in mice. Future studies of the underlying mechanisms might lead to potential therapies.

References:

Role of highly reactive aldehydes in cigarette smoke induced airway inflammation
Cigarette smoke (CS) is the most important cause of COPD, which is associated with chronic neutrophilic airway inflammation. We hypothesize, that the presence of highly reactive α,β-unsaturated aldehydes in CS is a crucial factor for neutrophilic airway inflammation.

Methods: BALB/c mice were exposed to CS, water filtered CS (WF-CS) or air. Levels of CO and aldehydes were measured in CS and WF-CS. Six hours after the last CS exposure, cell differentials and cytokine levels were measured in lung tissue and bronchoalveolar lavage fluid (BALF). Beas-2b cells (epithelial cell line) were exposed to cigarette smoke extract (CSE) or water filtered cigarette smoke extract (WF-CSE) with and without acrolein. The neutrophil chemotactant IL-8 was measured after 24 hrs.

CO levels were not different between CS and WF-CS but aldehyde levels were strongly decreased in WF-CS compared to CS. The numbers of neutrophils in BALF (p < 0.001) and neutrophils and eosinophils (p < 0.05) in lung tissue were significantly increased in the CS-exposed but not in WF-CS-exposed mice compared to air control. Levels of neutrophil and eosinophil chemotactants e.g. KC, MCP-1, MIP-1α and IL-5 were significantly increased in lung tissue from CS-exposed mice compared to WF-CS-exposed mice. Beas-2b cells produced significantly lower levels of IL-8 upon stimulation with CS but not in WF-CS-exposed cells compared to WF-CSE. Repletion of WF-CSE with the aldehyde acrolein restored the IL-8 production by Beas-2b cells whereas acrolein in culture medium did not. It can be concluded that highly reactive aldehydes present in cigarette smoke appear to play a crucial role in CS-induced IL-8 production and neutrophilic airway inflammation.

Effects of adipose tissue-derived stromal/stem cells transplantation on elastase-induced pulmonary emphysema in rats
Emphysema is the most common pathology in patients suffering from COPD. Emphysema results from alveolar destruction and obliteration of the alveoli. Data suggest that adipose tissue-derived stromal/stem cells (ASCs) for regenerative medicine, since it has a high potential to secrete multiple angiogenic factors and differentiate various kinds of cells. To demonstrate the therapeutic impact of ASCs transplantations and to elucidate mechanisms of the effects in rat emphysema models, ASCs were isolated from Wistar rat inguinal subcutaneous adipose tissue. Emphysema was induced by intratracheal instillation of porcine pancreatic elastase (PPE). One week after induction of PPE, cell transplantation was performed intravenously at 1 and 2 weeks after transplantation, we assessed arterial blood analysis and histopathological changes and measurement of chemokine levels. After PPE injection, arterial oxygen pressure (PaO2) was reduced. After ASCs transplantation, PaO2 significantly improved. In addition, transplantation significantly prevented the enlargement of alveolar airspace elicited by PPE. PPE gradually reduced the levels of endogenous hepatocyte growth factor (HGF) in lung tissue. ASCs augmented HGF level was significantly higher than PPE alone. ASCs from GFP transgenic rats were localized at damaged alveolar spaces. Immunohistochemical analysis revealed some grafted ASCs were expressed CD31 or SP-C at 1w after transplantation. The results showed that transplantation of ASCs for emphysema rats improved gas exchange and inhibited enlargement of the airspaces. Transplantation of ASCs may be a new therapeutic strategy to improve pulmonary function and inhibit alveolar destruction in COPD.

Role of IL-1α and IL-1β in cigarette smoke-induced pulmonary inflammation and COPD
Cigarette smoke is the most important cause of COPD, which is associated with chronic neutrophilic airway inflammation. We hypothesize, that the presence of highly reactive α,β-unsaturated aldehydes in CS is a crucial factor for neutrophilic airway inflammation.
presence of inflammatory cells in the bronchoalveolar lavage (BAL) fluid. In a translational study, we measured the levels of IL-1α and IL-1β mRNA (in total lung tissue by RT-PCR) and protein (in induced sputum by ELISA) of never smokers, smokers without COPD and patients with COPD. Acute exposure to CS resulted in a significant increase in BAL neutrophils in in vitro treated mice. In contrast, this CS-induced BAL neutrophilia was significantly attenuated in both anti-IL-1β and anti-IL-1α treated mice. Interestingly, we found increased mRNA and protein levels of IL-1α and IL-1β in lung tissue and induced sputum of patients with COPD, compared to never-smokers (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Human IL-1α and IL-1β levels</th>
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<td>Lung mRNA</td>
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<td>IL-1β</td>
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<td>Spinal protein (pg/ml)</td>
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*p<0.05 vs. never-smokers, *p<0.05 vs. smokers without COPD.

These results suggest that not only IL-1β, but also IL-1α should be considered important in CS-induced inflammation.

P3834

β2 long-acting and anticholinergic drugs synergistically control TGFβ1-mediated neutrophilic inflammation in COPD: An “in vitro” model

Patricia Macedo1, Iain Kilty2, Peter Barnes1, Louise Donnelly1.

Results: The addition of simvastatin at 5 μM in combination with either olodaterol or tiotropium reduced all 3 CXCR3 chemokines in PBMC from COPD patients, compared to PBMC from healthy controls (p=0.01). However, there were no differences in response to JAK inhibition between subject groups. JAK inhibitors PP95 and PP13 significantly suppress steroid-insensitive CXCR3 chemokines in COPD cells and may have benefit as a novel anti-inflammatory treatment.

P3836

Simvastatin attenuates cigarette smoke induced extracellular matrix Brian Oliver, Janette Burgess, Judy Black, David Krimmer. Cell Biology, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia

Introduction: Production of extracellular matrix (ECM) proteins is increased in the small airway walls of patients with chronic obstructive pulmonary disease (COPD). Current pharmacotherapies are unable to reduce or attenuate ECM in vivo. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, is emerging as a new potential therapy for COPD. In this study we investigated if simvastatin could affect cigarette smoke extract (CSE) induced ECM and cytokine production from human lung fibroblasts.

Methods: Primary human lung fibroblasts were stimulated with 5% CSE in the presence of 0.5 and 5μg/ml simvastatin, or relevant concentrations of vehicle control, for 72 hours. Supernatants were collected and assessed for pro-inflammatory cytokine and matrix metalloproteinase (MMP) release. Cells were removed by addition of NIH40 and the relative deposition of the ECM proteins fibronectin and perlecan was measured using an ECM ELISA. The concentration of interleukin (IL)-6, a marker of ECM deposition, was measured using ELISA.

Results: Treatment of human lung fibroblasts with 5% CSE upregulated the deposition of fibronectin and perlecan, and the release of IL-6 into the supernatant. Addition of simvastatin at 5μg/ml significantly attenuated 5% CSE induced deposition of fibronectin by 43% and perlecan by 41.5% (p<0.05, n=6). 5% CSE induced IL-6 release was also attenuated by 31% with the addition of simvastatin at 5μg/ml.

Conclusions: Inhibition of the HMG-CoA reductase pathway may alter the deposition of ECM proteins and release of inflammatory cytokines in COPD.

P3837

Sirtuin 1 reduction causes activation of Wnt/b-catenin signalling Andriana Papaioannou1,2, Konstantinos Kostikas3, Peter Barnes1, Kazuhiro Ito1.

Background: The anti-aging molecule Sirtuin 1 (SIRT1) has been reported to be decreased in COPD (Nakamura et al, FASEB J, 2009). We have also reported an increase of osteoprotegerin (OPG) in COPD (To M et al, CHEST 2011), which is b-catenin dependent. Our hypothesis is that the reduction of SIRT1 induced by oxidative stress may lead to increased b-catenin activation.

Methods: U937 (human monocytic cell line), AS49 (human alveolar epithelial cell line) and BEAS2B (human bronchial epithelial cell line) were grown until 70% confluent, starved for 24h and incubated with 2μM of sirtinol at 4 different time points (i.e. 1h, 4h, 8h, and 24h). The levels of b-catenin were measured in nuclear and cytoplasmic extracts by Western Blotting. Cells were also treated with H2O2 for 24 hrs and sirt1-1 protein level was also evaluated.

Results: The level of b-catenin was higher in AS49 and BEAS2B cells than U937 cells at baseline. In all three cell lines, nuclear b-catenin levels increased at 8h after treatment with 2μM of sirtinol by approximately 52% for the AS49 and 25% for the BEAS2B cells. No difference was detected in cytoplasmic b-catenin levels in any cell line. Incubation with H2O2 for 24h caused reduction in Sirt-1 levels in the AS49 cells.

Conclusions: This study shows that reduced SIRT1 protein leads to stabilization of β-catenin protein. This might give new insights in the understanding of COPD pathogenesis.

P3838

Role of aberrant Wnt signalling in the lung epithelial response to cigarette smoke in COPD

Irene Heijink1,2, Harold De Bruin1, Maarten Van den Berg1, Reinoud Gouwens1, Antoon Van Oosterhout1, Dirkje Postma2.

Background: This study shows that reduced SIRT1 protein leads to stabilization of β-catenin protein. This might give new insights in the understanding of COPD pathogenesis.

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leads to different phenotypes of COPD, i.e. inflammation and remodelling with increased extracellular matrix (ECM) deposition in the airways and loss of ECM in the parenchyma. The Wnt signaling pathway is known to regulate inflammation, tissue repair and remodelling. We aimed to determine whether dysregulation of Wnt genes may contribute to COPD development. We studied the effects of cigarette smoke extract (CSE, 5%) on expression of a variety of Wnt ligands, Wnt receptors (frizzled, Fzd) and Wnt target genes, including IL-8, MMP-2/9 and fibrotenon (pQPCR, ELISA, immunodetection) in alveolar A549 and human bronchial epithelial 16HBE cells. Furthermore, we compared expression of Wnt genes in primary bronchial epithelium from COPD patients, healthy smokers and non-smokers. CSE induced Wnt4, Wnt7b and FzdA mRNA expression in A549 cells, without significant changes in the other detected genes, i.e. Wnt5b, Fzd1 and 2 and MMP-2. In contrast, CSE significantly decreased Wnt4 and Fzd2, and increased Wnt5b mRNA in 16HBE cells. Interestingly, expression of Wnt5, but none of the other detected genes, was significantly higher in COPD than in healthy smoker epithelium. Therefore, we were interested in potential autocrine effects of Wnt4. We observed that recombinant Wnt4 significantly increased IL-8 production in 16HBE cells. Thus, inefficient downregulation of Wnt4 mRNA expression in response to cigarette smoke may have important consequences for the development and remodelling in COPD. Furthermore, our results suggest that Wnt4 differentially affects Wnt gene expression in alveolar and bronchial epithelium.

407. Immunology and cell biology of asthma and COPD

P3840 Disease and stimulus specific pro-inflammatory cytokine secretion by human fibroblast of asthma patients

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It is well documented that the asthmatic lung contains increased levels of pro-inflammatory cytokines. We provide evidence that healthy primary human fibroblasts isolated from medium size airways of asthma patients secrete significantly more IL-8 than in a stimulus and disease specific pattern. Bronchial fibroblasts from 5 asthma patients and 5 healthy controls were isolated and stimulated with PDGF-BB, TNF-alpha or IL-1beta (0.1, 1.0, 10 ng/ml), all of which are well known pro-inflammatory factors. After 24 hours, secreted IL-6, IL-8, eotaxin and GM-CSF were determined in the cell culture medium. PDGF-BB dose dependently increased both IL-6 and eotaxin secretion by 3 and 6 fold, respectively, but with no difference between asthma and control. In contrast, IL-8 and GM-CSF levels were significantly increased in asthma fibroblasts relative to control. IL-8 secretion dose dependently increased after TNF-alpha treatment, but no difference between asthma and control was observed. IL-1beta dose-dependently increased the secretion of all 4 cytokines, however, with a dose specific increase of GM-CSF at 10 ng/ml. Our data suggest that bronchial fibroblasts contribute to chronic inflammation in asthma in a disease and stimulus specific pattern.

P3841 The role of MKK3 in allergic and non-allergic inflammatory responses in the lung

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MKK3 is a member of the p38 MAPK signaling pathway and is an important factor in non allergic inflammation and Th1 responses. Less is known about the role of MKK3 in allergic inflammation. We investigated the role of MKK3 in murine models of non-allergic and allergic lung inflammation. Wild Type (WT) mice were instillated with lipopolysaccharide (LPS) (10 μg, i.t) or zymosan (100 μg i.t.). A significant increase in neutrophil numbers in the lung were observed 24h later compared to saline controls (saline: 0±6.01 x 10^6; WT: 9±6.4 x 10^6; n=5, p≤0.05). WT mice also produced significantly less TNF-α and INF-γ as compared to saline mice. MKK3-/- mice did not release these cytokines in response to LPS or zymosan. WT mice were sensitized twice to ovalbumin (ova, 10μg/mouse i.p in alun). From day 14 all mice were exposed to 3% ova once daily for 3 days. Lung lavages were performed 24 h after the last exposure. Exposure to ova significantly increased eosinophil numbers in the lungs of ova-sensitized mice as compared with sham-immunized mice (sham: 0±6.01 x 10^6; ova WT: 0±6.01 x 10^6; n=11; ova WT-/-: 2±6.01 x 10^6; n=10). WT mice showed significant increase of IL-5 compared to ova WT and sham-immunized mice (sham: 0±5.01 x 10^6; ova WT: 6±5.01 x 10^6; n=11; ova WT-/-: 12±5.01 x 10^6; n=10). WT mice also produced significant levels of IL-12, IL-6 and TNF-α as compared with sham-immunized mice (sham: 0.3±0.11 x 10^5/ml, n=9; ova WT: 1±0.11 x 10^5/ml, n=10). Ova-MKK3-/- mice showed significantly increased IL-5 compared to WT ova mice and sham-immunized mice (sham: 0±3.0±0.8 x 10^5/ml ova WT: 3±5.1±0.9 x 10^5/ml; ova WT-MKK3-/-: 8±5.1±0.9 x 10^5/ml). Ova-MKK3-/- mice showed significantly higher levels of IgE compared to WT mice, irrespective of ova treatment (sham WT: 0±6.01 x 10^6; ova WT: 6±6.01 x 10^6; n=6, sham MKK3-/-: 4±4.1±5.6 x 10^6; ova MKK3-/-: 5±3.8±4.5 x 10^6). In conclusion, MKK3 differentially regulates allergic and non-allergic responses in the lung.
activity and obesity. Leptin is an adipokine with a well-established functional role on airways function. The specific airway resistance (sRaw) and isolated bronchial rings reactivity were assessed on obese resistant (OR) and obese prone (OP) rats, fed with highfat diet. Results were compared with data from Sprague Dawley (SD) rats fed with standard diet. In vitro experiments were performed on main left bronchus rings. Both contraction induced by 10 μM acetylcholine (ACh) and terbutaline-induced relaxation were assessed. On OP bronchi, the terbutaline-induced dose-response curve was shifted to the right and the maximal relaxant effect was decreased up to 20%. Leptin pretreatment did not significantly modify terbutaline relaxant effects on OR but restored terbutaline effects on OP bronchi. Inhibition of all NO synthases (NOS) with 10 μM L-NAME reduced the bronchial relaxation. A number of studies have shown that adipokines have a role on airways function. The specific airway resistance (sRaw) and isolated bronchial rings reactivity were assessed on obese resistant (OR) and obese prone (OP) rats, fed with highfat diet. Results were compared with data from Sprague Dawley (SD) rats fed with standard diet. In vitro experiments were performed on main left bronchus rings. Both contraction induced by 10 μM acetylcholine (ACh) and terbutaline-induced relaxation were assessed. On OP bronchi, the terbutaline-induced dose-response curve was shifted to the right and the maximal relaxant effect was decreased up to 20%. Leptin pretreatment did not significantly modify terbutaline relaxant effects on OR but restored terbutaline effects on OP bronchi. Inhibition of all NO synthases (NOS) with 10 μM L-NAME reduced the bronchial relaxation. A number of studies have shown that adipokines have a role on airways function. 

### Conclusion

**Comorbidity digestive system diseases in patients with BA are associated with significant decrease of activity of cell and humoral parts of immune system.**

**P3846**

**Increased levels of CD4+CD25high and CD4+FoxP3+ T-regulatory cells (Tregs) in patients with different severity of bronchial asthma (BA)**

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**Background:** BA is characterized by persistent inflammation in the airways in response to allergens or other triggers. The intensity of the inflammation determines the severity of asthma. The level of anti-IgE responses and maintaining peripheral tolerance. Our study sought to determine whether numbers of CD4+CD25high and CD4+FoxP3+ Tregs are related to anti-IgE inflammation and disease severity.

**Aim and objectives:** To investigate the expression of surface molecules on Tregs in patients with different severity of bronchial asthma compared to healthy persons.

**Methods:** Peripheral blood mononuclear cells of control (n=17) and asthmatic patients (mild BA, n=11; severe BA, n=17) were labeled for CD4, CD25 and intracellular FoxP3 and analysed using flow cytometry.

**Results:** Numbers of peripheral blood CD4+CD25high was significantly decreased in asthmatic patients compared to healthy control patient. Patients with severe asthma had increased levels of CD4+CD25high and CD4+FoxP3+ compared to mild BA.

**Conclusions:** Our findings suggest that decreased levels of Tregs in peripheral blood might contribute airway inflammation. Increase CD4+CD25high and CD4+FoxP3+ is important in balancing immune responses for prevention the severity of asthma.

**P3847**

**Superoxide dismutase as a longitudinal biomarker of lung function in asthma**

Stury Comhair, Anam Khan, Serpi Elizur, Lehrer Research, Pathobiology, Cleveland Clinic, Cleveland, OH, United States

Asthma is a chronic inflammatory disease related to oxidative stress. Previously, we reported that superoxide dismutase (SOD) is lower in asthma as compared to healthy controls and related to airflow obstruction and reactivity. In this study, we hypothesized that serum SOD would be informative for progression of asthma over time. To test this, asthmatic adults with >10 years of disease duration were included. These results suggest that asthmatics with high SOD experience a progressive loss of lung function over time and are at risk for accelerated loss of lung function.

### Conclusion

**Superoxide dismutase as a longitudinal biomarker of lung function in asthma.**

Anna Maria Riccio1, Roberto Walter Dal Negro2, Laura De Ferrari1, Claudio Micheletto3, Giorgio Walter Canonica4, Chiara Foli5, Alessandra Chiappetta1, Dept. of Internal Medicine, Allergy and Respiratory Diseases, University of Genoa, Genoa, Italy; 2Dept. of Pulmonology, University Policlinico of Orlandi Hospital, Bussolengo, Verona, Italy

Asthma is a chronic inflammatory disease related to oxidative stress. Previously, we reported that superoxide dismutase (SOD) is lower in asthma as compared to healthy controls and related to airflow obstruction and reactivity. In this study, we hypothesized that serum SOD would be informative for progression of asthma over time. To test this, asthmatic adults with >10 years of disease duration were included. These results suggest that asthmatics with high SOD experience a progressive loss of lung function over time and are at risk for accelerated loss of lung function.

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tion in RBM thickness and different cut-off. The difference between Responder and Non-Responders proved statistically significant. Present data showed that 9/11 patients reduced the original RIM after treatment with anti-ILgE, thus emphasizing the role of omalizumab in affecting asthma remodeling.

P3849
Reverber is a novel regulator of COPD macrophage inflammation and glucocorticoid resistance
John Blackburn1, Julie Gibbs2, Andrew Louden3, Stuart Farrar3, Dave Singh1, David Ray1, 1Medicine, University of Manchester, Manchester, United Kingdom; 2Life Sciences, University of Manchester, Manchester, United Kingdom; 3Respiratory Center of Excellence for Drug Discovery, GSK, Stevenage, United Kingdom

Introduction: Human inflammation shows circadian oscillation of inflammatory mediators e.g., IL-8. The function of many anti-inflammatory drugs e.g. glucocorticoids also oscillate in a similar manner. The mechanisms causing these phenomena are poorly understood. A recent discovery describes that cells have a “molecular clock”, regulating 10% of the genome.

Aims: We investigated the function and mechanism of Reverber, part of this “molecular clock”, concerning COPD inflammation.

Results: LPS stimulated macrophages showed a diurnal response for IL-6. A novel Reverber ligand (GSK414112) corrected this but had no effect if Reverber expression was suppressed. The ligand had no effect in two epithelial cell lines (AS49, Hela), demonstrating cell specific actions. An array and luminex analysis on cellular supernatants from human healthy and COPD macrophages defined the targets and mechanism of GSK414112 suppression. A number of key COPD targets were suppressed. GSK414112 upregulated PPARα and LXRα, two nuclear receptors, and their respective cholesterol target genes e.g. ABCA1. A diurnal regulatory element analysis identified the importance of the LXR-DR4 motif, which Reverber binds. This mechanism was confirmed experimentally with a LXR antagonist. Luciferase reporter constructs, focused on the IL-6 proximal promoter, identified four LXR binding sites in the cell specific effect of Reverber, an activating factor binding site. GSK414112 doubled the IC50 of dexamethasone on IL-8.

Conclusion: Reverber affects both inflammation and glucocorticoid resistance. Synthetic ligands can modify its function potentially allowing for the first time to potential study inflammatory alterations that might increase the risk of developing lung cancer.

P3850
Quantitative proteomics study reveals cross-talk between autophagy and inflammation induced by cigarette smoke in airway cells
Yan Zhang1, Shen Yingchun1, Wen Yang1, Wang Tao1, Xin Dan1, Chen Lei. 1Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China and Dept. of Respiratory Medicine, 2National Key Laboratory of Novel Drug and Cancer Center, 3Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Introduction: Cigarette smoke (CS) is an important risk factor for the development of airway inflammation. Autophagy can be induced by CS, while the role of autophagy in airway inflammation induced by CS was still unclear. We sought to determine the role of autophagy in cigarette smoke induced airway inflammation induced by CS using system-level analysis by amino acids in cell culture (SILAC)-based quantitative proteomics.

Methods: SILAC-labeled human lung mucocoeidometer cells (NCI-H292) was exposed to cigarette smoke extract for 24h, and then was used to identify the differentially expressed proteins. In order to validate the results in vivo, rats were exposed to CS for 4 weeks. Besides the analysis of bronchoalveolar lavage fluid (BALF) and histological changes, immunohistochemistry and western blot validated the selected proteins. Autophagy was observed by electron microscope (EM).

Results: Three proteins associated with autophagy were significantly up-regulated after CS exposure in NCI-H292 cell (p<0.05), including macrophage-associated protease 1A/1B light chain 3C(LC3A/B), high mobility group protein (HMGB1), and Cystatin-C. EM revealed that autophagic vacuoles were dramatically increased in rat lung tissues exposed to CS (p<0.05). Moreover, airway inflammation induced by CS was demonstrated by histological changes, increased cell counts and proinflammatory cytokines in BALF (respectively, p<0.05, p<0.05). Immunohistochemistry and western blot demonstrated that CS markedly increased LC3A/B, Cystatin-C and HMGB1 expression in rat lung (respectively, p<0.05).

Conclusions: Autophagy may play a role in cigarette smoke induced inflammation by CS.

P3851
Myeloid derived suppressor cells in the crosstalk between COPD and lung cancer
Simone Baraldo1, Laura Pinton2, Andrea Ballarin1, Susanna Mandruzzato2, Laura Pinton1, Ying Binwu1, Wang Tao1, Xu Dan1, Chen Lei, 1Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China and Dept. of Respiratory Medicine, 2National Key Laboratory of Novel Drug and Cancer Center, 3Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Introduction: Myeloid derived suppressor cells (MDSC) are poorly understood. A recent discovery describes that cells have a "molecular clock", regulating 10% of the genome.

Background: Inhaled corticosteroids are recommended for COPD patients with FEV1 ≤ 50% predicted, experiencing ≥2 exacerbations in 12 months. However, post-hoc analysis of the TORCH study revealed an increased risk of pneumonia of 50% in patients taking inhaled corticosteroids compared to the Cefuroxime prophylactic (CFP) (ERJ 2009:34:641).

Results: BUD (1µM) increased MDSC phagocytosis of beads by 17% (p<0.05), whereas FP had no effect. Neither steroid altered MDM phagocytosis of either HI or SP. Neither steroid altered neutrophil phagocytosis of beads or SP. In contrast, BUD (10µM,100µM) significantly (p<0.05) increased neutrophil phagocytosis of HI with a maximal effect of 67%. FP (1µM) showed a smaller effect, increasing phagocytosis of HI by 38% (p<0.05).

Conclusions: FP did not reduce phagocytic function of either MDM or neutrophils.

P3853
IL-17A expression by mast cells in smokers
Yvonne Nussbaumer-Ochsner1, Luz F. Ferrar da Silva2, Klaus F. Rabe1,1, Annemarie M. van Schadewijk1,2, Pieter S. Hiemstra1,1

1Airways Disease, NHLI, Imperial College, London, United Kingdom; 2Astra Zeneica R&D Lund, AZ, Lund, Sweden

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Methods: Neutrophils and monocytes were isolated from the blood of COPD patients (n=10). Monocyte-derived macrophages (MDM) were generated from monocytes by 12d culture in media containing GM-CSF. All cells were incubated with steroid for 1h prior to phagocytosis assays with fluorescently labelled polyethylene beads, Haemophilus influenzae (HI) or Streptococcus pneumoniae (SP).

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Conclusions: FP did not reduce phagocytic function of either MDM or neutrophils.

BUD improved neutrophil phagocytosis of HI, which may explain differences in pneumonia incidence between FP and BUD in COPD patients.
Abstract P3853 – Table 1

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<td>SA inner</td>
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<td>outer</td>
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N=12. Medians (quartiles). *p<0.05 vs corresponding SA layer within same cell type. ±p<0.05 vs corresponding outer layer within same airway type.

P3854 Carbocysteine and N-acetyl cysteine inhibit cigarette smoke mediated acetylation of the PMN chemotractant peptide PGP

Michael Brown, Matthew Harding, Edwin Blalock, Patricia Jackson. Pulmonary Division, University of Alabama at Birmingham, Birmingham, AL, United States

Cigarette smoke contains reactive compounds that result in epithelial damage and stimulate neutrophil chemotaxis, airway inflammation, and collagen breakdown. Proline-Glycine-Proline (PGP) is a degradation product of collagen proteolysis. PGP activates neutrophil receptors stimulating further chemotaxis and inflammation. PGP and an N-terminal acetylated PGP (NacPGP) are elevated in clinical samples of COPD patients and correlate with disease activity. NacPGP confers increased potency for neutrophil stimulation and bioavailability as leukotriene A4 Hydrolase responsible for PGP destruction, is incapable of acting on NacPGP.

N-acetyl cysteine (NAC) and carbocysteine (CC) are scavengers of reactive compounds and used as mucolytics in chronic lung diseases. We hypothesize that NAC and/or CC will prevent PGP acetylation by cigarette smoke. These compounds may provide better understanding of targeted therapeutics in cigarette smoking-related lung disease.

Cigarette smoke extract (CSE) or condensate (CSC) was prepared and incubated with native PGP. / NAC or CC. Samples were incubated and analyzed for CSE or NacPGP. NacPGP concentration was measured with mass spectrometry. This data was repeated in a vapor experiment, where PGP mixed with either NAC or CC was placed in a separate well from cigarette smoke in a 96-well plate and incubated. Our data demonstrate that PGP generation by cigarette smoke extract, condensate, and vapor that is inhibited by NAC or CC. Our data support a possible mechanism where reducing compounds such as NAC and CC may diminish lung inflammation in COPD and other chronic lung diseases by inhibiting PGP acetylation thereby facilitating PGP degradation.

P3855 Interactions between the effects of a 4-week NO2 and carbon nanoparticle exposure with allergen sensitization on bronchial responsiveness in Brown Norway rats

Skander Layachi,1 François Rogerieux,2 Christelle Gamez,2 Kelly Blazy,2 Francck Robidel,2 Anthony Lecomte,2 Ghislaine Lacroix,2 Sam Bayat,1,3 1E44285 - INERIS UMR01, INERIS, Verneuil-en-Halatte, France; 2Pulmonary Physiology Laboratory, CHU Amiens, Amiens, France; 3Paediatric Lung Function Laboratory, CHU Amiens, Amiens, France

Aims: The aim of this study was to assess the effect of combinations of allergen sensitization, NO2 and carbon nanoparticle (CNP) exposure on airway reactivity (AR).

Methods: Brown-Norway rats were divided into the following groups: Control; NO2; CNP + NO2. Human lung fibroblasts were stimulated for up to 72 hours with increasing concentrations of biomass smoke extract (BME) or cigarette smoke extract (CSE) as a comparison. Cells were lysed and deposition of ECM proteins was measured using western blotting. Release of interleukin (IL)-8 was determined using an ELISA assay. Cell viability was assessed using manual cell counts and a commercially available MTT assay.

Results: The deposition of the ECM proteins fibronectin and fibronectin increases with increasing concentration of biomass smoke extract (BME) or cigarette smoke extract (CSE) as a comparison. Cells were lysed and deposition of ECM proteins was measured using western blotting. Release of interleukin (IL)-8 was determined using an ELISA assay. Cell viability was assessed using manual cell counts and a commercially available MTT assay.

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P3856 Biomass smoke extract increases fibronectin and perlecan release from human lung fibroblasts

Brian Oliver, Janette Burgess, Judy Black, David Krimmer. Cell Biology, Woolcock Institute of Medical Research, The University of Sydney, Sydney, Australia

Introduction: Approximately 50% of deaths from chronic obstructive pulmonary disease (COPD) in developing countries have resulted from repeated exposure to burning biomass, such as is used in household cooking. Biomass-induced COPD has been reported to be associated with a more fibrotic phenotype than cigarette smoke induced COPD. We aimed to investigate if biomass smoke induced extracellular matrix (ECM) protein production from primary human lung cells in vitro.

Methods: Primary human lung fibroblasts were stimulated for up to 72 hours with increasing concentrations of biomass smoke extract (BME) or cigarette smoke extract (CSE) as a comparison. Cells were lysed and deposition of ECM proteins was measured using western blotting. Release of interleukin (IL)-8 was determined using an ELISA assay. Cell viability was assessed using manual cell counts and a commercially available MTT assay.

Results: The deposition of the ECM proteins perlecan and fibronectin was upregulated by both 5% CSE and 1% BME, 1%, 5%, 10% and 20% BME and 5% CSE significantly upregulated the phosphorylation of ERK1 and ERK2 following 30 minutes exposure and these remained elevated to 24 hours exposure. Release of IL-8 in the supernatant was increased by 5% CSE and 1% BME. Exposure to concentrations of BME >10% caused significant decreases in cell viability.

Conclusion: BME has similar effects to CSE in vitro and in vivo.

Ozone is an oxidizing environmental pollutant that significantly contributes to respiratory health risk. Exposure to increased ambient levels of ozone has been associated with worsening of symptoms of patients with lung diseases like asthma and COPD. In this study we investigate the chronic effects of ozone exposure on Hypoxia Inducible Factor (HIF)-1α binding to HIF1α and HIF1α promoter regions associated with changes in gene expression levels in chronic ozone exposed mice.

Brian Oliver, Kirsty Russell, Colin Clarke, Peter Barnes, Ian Adcock. Airway Disease Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom

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P3858
Characterisation of T cell populations in proximal and distal airways
Rebecca Spence, Gregory Rankin, Christopher Pickard, Jane Warner. School of Medicine, University of Southampton, Southampton, Hampshire, United Kingdom

Introduction: CD4+ T cells are known to be involved in the pathogenesis of COPD but their distribution in COPD is unknown. We have characterised T cell populations from the distal and proximal airways of patients with and without airways obstruction.

Methods: Macrophageinflamed normal matched proximal and distal airway tissue was obtained from 23 patients (mean age 66±2.7 years, FEV1/FVC=0.66±0.02) undergoing lung resection. Samples were dissected into explants, fixed and processed for GMA immunohistochemistry. Sections were stained for CD3, CD4 and CD8.

To examine a larger population of T cells, explants from the same patients were incubated for 24 hours to encourage T cell migration into supernatant. Recovered cells were stained for T cell markers (CD3-FITC, CD8-APC) and analyzed via FACs.

Results: Immunohistochemical analysis revealed relatively few T cells in either proximal or distal airways (median CD3+ cells distal airways =1.6/mm2 compared to proximal airways). Immunohistochemical analysis revealed relatively few T cells in either proximal or distal airways (median CD3+ cells distal airways =1.6/mm2 compared to proximal airways). CD4+ cells were predominant in the distal airways while the distribution was not significantly affected by the presence of airways obstruction.

Conclusions: Similar numbers of CD3+ cells were found in the proximal and distal airways. CD4+ cells were predominant in the distal airways while the distribution of CD4 and CD8+ cells was equivalent in the proximal airways. The presence of mild/moderate COPD did not affect T cell number or distribution.

408. Phagocytes and dendritic cells

P3859
Characterisation of a new Daisy cell line representative of human alveolar macrophage (hAM)
Yvette Hayman, Simon Hart, Alyon Morice. Academic Cardiovacular and Respiratory Medicine, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom

Introduction: Techniques used to obtain primary hAM are invasive, often providing low yields which cannot be expanded in vitro. No human cell line exists in an alternative. We characterised a new human cell line capable of expansion and spontaneous differentiation.

Methods: Cells were cultured in RPMI1640 with 10% foetal bovine serum and penicillin/streptomycin (100U/ml)10ng/ml in a humidified 5% CO2 atmosphere, passed every 2 days. Light and transmission electron microscopy comparing Daisy cells with THP-1 cells stimulated with phorbol myristate acetate (PMA;50ng/ml;24h) was performed. Flow cytometric immunophenotyping studies were performed analysing CD 11b, 14, 16, 23, 24, 32, 36, 64, 163 and 206 expression. Results were compared with both THP-1 cells and primary hAM obtained by bronchoalveolar lavage. Phagocytic capacity by zymosan uptake (mg/ml), mycospora screening by fluorescence microscopy and opsonised antigen binding by flow cytometry were also assessed.

Results: Microscopy showed Daisy cells to be similar in size, shape and granularity to PMA stimulated THP-1 cells with a higher proportion of heterochromatin, pseudopodia and vesicular inclusions. Daisy cells were shown to express lower levels of CD11b, 14 and 32 compared with PMA stimulated THP-1 cells yet higher levels of CD66, 80, 163 and 206. CD marker expression of Daisy cells more closely resembled that of primary hAM. Zymosan was readily phagocytosed, mycospora was not detected and high levels of opsonised antigen binding were seen in Daisy but not THP-1 cells.

Conclusions: The new Daisy cell line shows characteristics of mature hAM yet can be maintained and cultured providing a useful tool in respiratory research.

P3860
Sirtuins, the anti-ageing molecules, regulate anti-oxidant capacity via FoxO3 activity in monocyte cell line
Laura Nunez Naveira, Nicolas Mercado, Kazuhiro Is. Airway Disease, National Heart and Lung Institute (NHLI). Imperial College, London, United Kingdom

Chronic Obstructive Pulmonary Disease (COPD) is characterized by high levels of oxidative stress due to reduced anti-oxidative stress capacity, leading to an increase of oxidative stress. Sirtuins, type III histone deacetylases, have been linked to chronic obstructive pulmonary disease (COPD). These proteins are involved in the maintenance of nuclear function and are involved in the regulation of various cellular processes such as aging, lipid metabolism and inflammation.

Methods: Human peripheral blood mononuclear cells (PBMC) were cultured in the presence of reverse transcriptase polymerase chain reaction (RT-PCR) or luciferase assay for FoxO3 activity and sirtuin expression. The effect of sirtuin activation on FoxO3 activity was assessed using RNA interference (RNAi) and pharmacological inhibitors.

Results: The activation of sirtuin 1 (SIRT1) and 2 (SIRT2) increased FoxO3 activity, while the activation of SIRT3 and 6 (SIRT3 and 6) had no effect. The activation of SIRT1 and 2 also increased the expression of anti-oxidant genes such as MnSOD and NQO1.

Conclusions: Sirtuins play a key role in the regulation of anti-oxidant capacity via FoxO3 activity. The activation of SIRT1 and 2 may be a potential therapeutic target for treating COPD.

P3861
YKL-40: Novel marker for pro-inflammatory M1 macrophages
Elodie Kunz, Emily van ‘t Wout, Annemarie van Schadewijk, Pieter Hielstra. Pulmonary, Leiden University Medical Center, Leiden, Netherlands

Macrophages play a major role in the pathogenesis of COPD and comprise a heterogeneous cell population with pro- (M1) and anti-inflammatory (M2) cells. CD163 has been identified as a M2 marker, however, many M1 markers are not suitable for analysis. Cells positive for YKL-40, a chitinase-like-protein, are elevated in the lungs of smoking than non-smoking COPD patients. Dexamethasone strongly reduces YKL-40 expression in peripheral blood mononuclear cells in vitro, suggesting that it is a potential therapeutic target for treating COPD.

Methods: PMA stimulated THP-1 cells showed maximal lipid accumulation in vitro, indicating that inhaled steroids in COPD may decrease YKL-40 expression. Dexamethasone dose-dependently and strongly inhibited YKL-40 expression in both M1 and M2 (p<0.05).

Conclusions: YKL-40 expression can be used as a marker for M1 macrophages in vitro, and possibly in vivo.

P3862
Lipid laden alveolar macrophages arise from airway reflux and aspiration
Yvette Hayman, Simon Hart, Alyon Morice. Academic Card iovascular and Respiratory Medicine, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom

Introduction: Lipid laden macrophages have previously been reported to be present in the diseased human airway, secondary to gastro-oesophageal reflux. We investigated the possibility that the lipid index (LI) system of scoring cellular lipid content by oil red o (ORO) staining could correlate with disease status and the Hull Airway Reflux Questionnaire (HARQ). We also investigated the hypothesis that lipid could be ingested directly from gastric contents by alveolar macrophages.

Methods: Primary alveolar macrophages were obtained from bronchoalveolar lavage (BAL) fluid of patients undergoing diagnostic bronchoscopy. Patients were asked to fill in the HARQ prior to treatment. Lavage fluid was filtered and centrifuged (350g;10min.) and cells transferred to glass slides using cytopsin equipment. Cells were stained with ORO, counterstained with haematoxylin and macrophages scored according to the LI system. Meanwhile THP-1 cells stimulated to differentiate with phorbol myristate acetate (PMA;50ng/ml;24h) were incubated with varying concentrations of a high fat meal and a fat free liquid meal as a control.

Results: 18 patients with a range of respiratory diseases had LI scores ranging from 4 to 309. LI score correlates (r = 0.8) with the HARQ but not to a particular disease group. PMA stimulated THP-1 cells showed maximal lipid accumulation by ORO staining with 10% v/v high fat liquid meal for 24h. No lipid accumulation was seen with the control feed.

Conclusions: Lipid laden macrophages arise from airway reflux and aspiration. Lipid laden macrophages correlate with the presence of lipid laden macrophages in the airway.
P3863 Reprogramming of alveolar macrophages – Prospect of successful treatment in COPD
Svetlana Lyamina1, Igor Maev2, Georgy Yurenev2, Igor Malyshev1. 1Laboratory of Cell Biotechnologies, Moscow State University of Medicine and Dentistry, Moscow, Russian Federation; 2Department of Internal Diseases, Moscow State University of Medicine and Dentistry, Moscow, Russian Federation

Reprogramming of macrophages can be one of new promising approaches in nosotrophies, improving the balance of inflammatory reaction and allowing to reach the optimal Th1/Th2 balance in early pathologic process. 

Objective: To testify that serum concentration change with TGF-β as reprogramming factor in culture medium can purposefully reprogram macrophages phenotype either to M1 pro-inflammatory or to M2 anti-inflammatory and therefore influence Th1/Th2 balance.

Methods: Alveolar macrophages of COPD patients with initial M1 phenotype were cultivated and reprogrammed in vitro in RPMI-1640 with different serum concentrations – 5%, 10%, 15% for 48 hours. Reprogramming of macrophages was measured by morphological characteristic of cells with morphological index, expression level of cell markers CD80, CD25 (M1), CD206, CD163 (M2) and cytokine production by flow cytometry.

Results: Significant changes of morphological characteristic and functional activity were educed. Serum concentration change from 5% to 15% led to increasing of interleukin-like cells (from 24 to 85%), morphological index varied from 0.26 to 1.02; Th2 cytokines prevailed on Th1; CD206 and CD163 expression level significantly changed – 57% and 64% vs 21% and 29% respectively. These data confirm successful reprogramming of macrophages to M2 phenotype. In view of obtained data decreasing of serum concentration from 15% to 5% led to M1 phenotype reprogramming.

Conclusions: Serum concentration in cell culture promotes reprogramming of morphological and functional phenotype of alveolar macrophages, which can be used for reaching Th1/Th2 balance and regulation of lung immunity in COPD patients.

P3864 Lipid laden macrophages in patients with chronic cough
Begoña Palomo, Jose Belda, Miguel Arias, C.J. Rtguz. Pandiella, Paz Paniagua, Magdalena Rebollo, Per Caras. Neurology, INS-HUCA, Oriedo, Asturias, Spain

Background: Gastroesophageal reflux disease (GER) has been described as com-
mon cause of chronic cough by either esophageal acid-induced bronchoconstriction or recurrent microaspirations of gastric content. Lipid laden macrophages (LLM) in sputum may be a marker of aspiration. This finding could be interesting mainly when symptoms are absent (up to 75% percent or cases, “silent” GER). However, it is not clear what the presence of LLM in the airways could imply in terms of lung function, radiological lesions or symptoms. We aim to compare a group of patients with chronic cough and LLM in sputum with another group without LLM.

Methods: Twenty five patients with chronic cough that could not be attributed to any known etiology were included in the study group. Subjects were questioned for pulmonary and GER symptoms. Rhinitis, drugs and underwent physical ex-
amination, chest X-rays, bronchial challenge test with methacholine and sputum induction. Prepared cytospins were stained with oil red-O to detect lipid laden macrophages.

Results: 68% were lipid laden positive but only 40% had reflux symptoms. Pa-
tients with LLM had similar dyspnea, phlegm's but not rhinitis and 25% were methacholine positive and diagnosed of having asthma. Patients with LLM had radiological findings (mild lesions) in 60% of them and they had less FEV1 240 ml (11% of ref val) and FVC 364 ml (7% ref val) when adjusted by asthma and anamnestic characteristics.

Conclusions: The presence of LLM in sputum could represent worse pulmonary disease in patients with chronic cough even in absence of GER symptoms.

P3865 Effects of Bu-Zhong-Yi-Qi-Tang (Hocheukito; TJ-41) on the inflammatory responses in alveolar macrophages of hyperglycemic mice
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This study examines the influence of Bu-Zhong-Yi-Qi-Tang (Hocheukito; TJ-41) on the inflammatory response in alveolar macrophage in hyperglycemic mice. BALB/c mice (males, six to eight weeks old) were divided into three groups: A, B, and C. Group A, B and C were fed an ordinary diet, whereas TJ-41 was given to group C. After the initiation of these diets, intraperitoneal injection of streptozotocin (STZ), 250mg/kg in mice of groups B and C. Four weeks after the start of these diets, blood-glucose levels were measured, and bronchoalveolar lavage (BAL) was performed. Alveolar macrophages were sampled, and those demonstrating blood-glucose levels of more than 200 mg/dL were selected for use. Toll-like receptor (TLR) ligands (TLR2: peptidoglycan [PGN], TLR4: LPS, TLR5: flagellin [FLGI]) were employed to stimulate pulmonary-alveolar macrophage phagocytosis and ELISA was used to measure TNF-a production. TLR expression on pulmonary-alveoli surface was evaluated on the basis of the emergence of each TLR mRNA in alveolar macrophages. In mice given STZ, stimuli with TLR2, 5 ligands significantly inhibited TNF-a production. But in mice given a diet including TJ-41 inhibition of TNF-a production improved significantly. These differences were observed in the expression of TLR mRNA in pulmonary-alveolar macrophages and on cell surfaces. These results suggest the possibility that TJ-41 may enhance inhibition of pulmonary-alveolar macrophage inflammation response to TLR-ligands stimulus in conditions of high blood glucose.

P3866 LSC 2011 Abstract: Differential effects of diesel exhaust particles and endotoxin on phagocytosis and cytokine release by monocyte-derived macrophages
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Atmospheric pollution is associated with COPD exacerbations. Diesel exhaust particles (DEP) are major contributors to pollution and when inhaled become tar-
geted for lung macrophages. The immune response to DEP remains unclear. Monocyte-derived macrophages (MDM) from non-smokers (NS), smokers (S) or patients with COPD were exposed to DEP (1-300μg/ml) with or without bacterial endotoxin (LPS; 10μg/ml) for 24h. Release of TNF-a, IL-6 and CXCL8 was analysed by ELISA, and phagocytosis of fluorescent beads was assessed by flow cytometry. MDM viability was determined by MTT assay.

Exposure of MDM to DEP did not stimulate release of IL-6 or TNF-a but increased CXCL8 release (E/C, NS 8±4 μg/ml, n=7; S 4±1 μg/ml, n=4 and COPD 10±4 μg/ml, n=7). MDM from COPD patients were 3.3 times more responsive to DEP (30μg/ml; p<0.05) than cells from smokers. When MDM were stimulated with LPS, DEP did not alter TNF-a or CXCL8 release. However, DEP inhib-
ited LPS-stimulated release of IL-6 in cells from all subject groups (E/C: NS: 33±14 μg/ml, n=10; smokers: 25±15 μg/ml, n=4; COPD: 18±14 μg/ml, n=10). Exposure of MDM to DEP in both the absence and presence of LPS inhibited phagocytosis of beads in a concentration-dependent manner with 300μg/ml show-
ing ~90% inhibition (control: 31±3 X 10² vs 300μg/ml DEP: 6±1 X 10² RFU, n=29), with MDM being 70% viable at this concentration, with no difference in response between the different subject groups. These data show that DEP impair macrophage phagocytosis and promote chemokine release. These data suggest that DEP may lead to reduced clearance of debris and pathogens from airways and promote COPD exacerbations.

P3867 Changed phagocytic activity and pattern of Fcγ and complement receptors on blood monocytes in sarcoidosis
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We have recently revealed that mycobacterial heat shock proteins (Mtb-hp), in-
volved in forming of immune complexes (CI's), can induce immune response in sarcoidosis (SA). The complexity may result from inappropriate phagocytosis and clearance of CI's by monocytes, which results in persistent antigenemia and granuloma formation. It is also possible that aberrant expression of receptors for Fc fragment of immunoglobulin G (FcγR) and complement receptors (CR) on monocytes can be involved in this process.

To test this hypothesis, we have evaluated the expression of FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) and CR1 (CD35), CR3 (CD11b), CR4 (CD1c) receptors on blood monocytes on the basis of high antigen load, persistent antigenemia and complexemia in SA patients. To this hypothesis, we have evaluated the expression of FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) and CR1 (CD35), CR3 (CD11b), CR4 (CD1c) receptors on blood monocytes.

As compared to healthy controls, we found significantly increased expression of all examined FcγRI (CD32, CD16, CD64) and decreased expression of CD35 and CD1c on CD14+ monocytes in SA patients. Analysis of the combined phenotypes of monocytes revealed significantly increased percentage of CD14+CD16+CD35+, CD14+CD64+CD35+, CD14+CD64+CD11b+, CD14+CD64+CD11c+ monocytes and decreased presence of CD14+CD32+CD35+, CD14+CD32+CD11b+ and CD14+CD32+CD11c+ monocytes in SA vs controls. The total number and percentage of phagocytizing blood monocytes was significantly increased in SA as compared with healthy individuals.

In summary, altered expression of Fcγ and complement receptors on CD14+ monocytes and increased phagocytic activity of monocytes may be responsible for high antigen load, persistent antigenemia and complexemia in SA patients.

P3868 Immune complex binding by Fcγ receptor IIa and regulation of inflammation
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Immune complexes, mainly associated with autoimmune diseases, may also be

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present in the blood and lung during respiratory diseases including bacterial pneumonia and ARDS. However, the precise pathogenic role of immune complexes in these conditions is unknown. Binding of immune complexes to the uniquely human stimulatory IgG receptor FcγRIIA is constitutively suppressed on neutrophils and macrophages. Elucidating the mechanism behind this suppression will help us understand how the body regulates its response to immune complexes. The erythroleukemia cell line K562 that expresses the FcγIIA inherently and exhibits FcγRIIA suppression was used as a model. The effects of microbial neuraminidases on the ability of immune complexes binding by the FcγRIIA were tested by flow cytometry. We also investigated whether there is a protein in close proximity to FcγRIIA that could potentially block its IgG binding site by protein cross-linking. Lastly, the stimulatory character of the receptor was explored by calcium signaling. Although the receptor exhibits suppressed immune complex binding, microbial neuraminidases can significantly augment the ability of the FcγRIIA to bind immune complexes. The cross-linking experiments reveal that there is a protein in close proximity with FcγRIIA that could be blocking its IgG binding site under basal conditions. Finally, while FcγRIIA exhibits limited binding of immune complexes in its native state, the stimulatory signals produced by the receptor on contact with immune complexes are significantly strong. Understanding how the body regulates immune complexes could lead to identification of novel methods for both activating and inhibiting the progression of immune complex mediated inflammation.

P3869
Anti-inflammatory activity of macrolides in peripheral blood mononuclear cells and the identification of potential biomarkers of azithromycin administration
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Many studies in the recent past have determined that macrolide antibiotics have anti-inflammatory and immuno-modulatory activity in addition to their efficacy in treating bacterial infection. Macrolides have been successfully used in the treatment of diverse chronic inflammatory respiratory disorders, including diffuse panbronchiolitis (DPB), cystic fibrosis (CF) and bronchiolitis obliterans. We investigated the ability of azithromycin to attenuate the effects of a lymphocyte directed pro-inflammatory stimulus in PBMCs from healthy volunteers. Our results demonstrate that azithromycin significantly inhibited the induction of proliferation and the release of IL17 in these cells. Treatment with azithromycin in the absence of a pro-inflammatory stimulus in PBMCs induced the release of IL10 in a dose dependent manner 24 h after challenge. The same model, azithromycin caused a dose dependent decrease in GMSCF 24 h after treatment. In conclusion, azithromycin exhibits significant anti-inflammatory and immuno-modulatory properties and IL10 and GMCSF may prove to be useful biomarkers following macrolide therapy in respiratory disorders.

P3870
A novel macrolide/fluoroketolide, solithromycin (CEM-101), reverses corticosteroid insensitivity via activation of protein phosphatase PP2A
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Introduction: Activation of P3D kinase causes oxidative stress-induced corticos- teroid (CS) insensitivity via HDAC2 reduction. We have recently demonstrated that a novel macrolide/fluoroketolide, solithromycin (Soli, CEM-101) restores CS sensitivity via HDAC up-regulation due to PI3K signaling inhibition (ATS2010). However, the mechanism of this effect has not been elucidated.

Aims: To investigate the role of a serine/threonine phosphatase PP2A on regulation of the P38 pathway as the target of Soli.

Methods: CS sensitivity was determined by IC50 of dexamethasone (Dex) on TNFα-induced IL-8 production in U937 monocyte cell. Activities of HDAC2 and PP2A were measured by fluorescence-based assay phosphorylation levels of Akt as a marker of P38K activation were determined by Western blotting. Okadaic acid (OA) was used to inhibit PP2A as needed.

Results: OA enhanced H2O2-induced Akt phosphorylation and HDAC2 reduction in U937 cells, and recombinant PP2A reduced Akt phosphorylation levels. Soli restored Dex sensitivity under H2O2 exposure, but pretreatment with OA abrogated Soli-mediated restoration of Dex sensitivity, inhibition of Akt phosphorylation, and HDAC2 activation. In addition, PP2A immunoprecipitates from the membrane fraction and recombinant PP2A were directly activated by Soli.

Conclusions: PP2A might be a negative regulator of P38K signaling. Soli acti-

P3871
Exposure to cigarette smoke affects the response of dendritic cells to pneumococcus
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Development of chronic obstructive pulmonary disease (COPD) is linked to tabagism. Acute exacerbation potentially related to infection by streptococcus pneumoniae is responsible for the progression of the disease. Innate immunity asso-
ciated with dendritic cells (DC) mobilization is involved in the pathophysiology of the disease. We hypothesize that cigarette smoke impairs the response of DC to pathogens, a mechanism that may be involved in COPD progression.

Monocyte-derived DC of healthy donors were exposed to cigarette smoke extract (CSE) and next to its IgG binding site under basal conditions. Finally, while FcγRIIA exhibits limited binding of immune complexes in its native state, the stimulatory signals produced by the receptor on contact with immune complexes are significantly strong. Understanding how the body regulates immune complexes could lead to identification of novel methods for both activating and inhibiting the progression of immune complex mediated inflammation.

P3872
OM-85 shapes dendritic cell activation into a "pre-alert" phenotype
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Methods: Primary and in vitro derived hDC were used to determine the precise OM-85 effects on DC biology. Stably transfected cell lines expressing human immune receptors were used to characterize OM-85 receptor-dependent activity.

Results: In hDC, OM-85 induced the secretion of IL-6 and of several chemokines (i.e. CXCL8, CXCL4, CCL2) with a potency comparable to the prototypic activating stimulus LPS. OM-85 potentiated the effect of IFN-γ in terms of IL-6, IL-12 and IL-10 release. The induction of selected chemokines by suboptimal doses of classical pro-inflammatory stimuli were boosted by the presence of OM-85. In addition, it was identified that OM-85 activates TLR2, NOD1 and NOD2 receptors in a significant, dose-response manner. Conclusions: OM-85 induces a mild and well shaped DC activation through selected pattern recognition receptors. This activation may contribute to the gen-

P3873
Altered phenotype of blood dendritic cells in patients with acute pneumonia
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Background: Dendritic cells (DCs) play a key role in the host defense against inhalated pathogens. However, the phenotype of blood DCs in patients with acute infections is unknown.

Methods: Sixteen patients with an acute pneumonia and 19 controls without pneumonia were included in the study. The number as well as the expression of function-associated molecules of blood DCs in patients without acute infections pneumonia.

Results: Elevated concentrations of procalcitonin (median: 0.55 ng/ml) and the
rapid response to antibiotic treatment suggested a bacterial origin of the pneumonia in the patients. Total mDC (median: 27% of the controls) and pDC counts (median: 53% of the controls) were markedly reduced in patients with pneumonia, as compared to controls. Percentages of blood mDCs, but not pDCs, were negatively correlated with serum concentrations of C-reactive protein (CRP). Patients with pneumonia were characterised by a significantly increased expression of Fc gamma receptors (CD32 and CD64) on mDCs and the Toll-like receptor 9 (TLR9) in pDCs.

Conclusions: Circulating DCs are markedly reduced in patients with pneumonia, and characterized by an upregulation of molecules recognising pathogen-associated molecular patterns (PAMPs) and opsonised antigens.

P3874
Humanized Staphylococcus aureus (Fcγ) transfected non-small cell lung cancer (NSCLC) cells induce local inflammatory and necrotic changes in an experimental model
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Background: Tumors, including NSCLC, develop numerous local mechanisms which impair maturation of dendritic cells (DCs). The delivery of stimulatory signals to DCs from cancer microenvironment is believed to be an effective means to break tumor-induced tolerance.
Aim: Evaluation of immunostimulatory properties of TLR5 ligand, FicG, cell membrane-displayed in experimental model of Lewis Lung Cancer (LLC) transfected with a novel plasmid vector system.
Methods: Cell membrane-expressed humanized FicG transgene was inserted to the pCDNA3.1Zeo+ plasmid-based construct. Tumor specific two-step transcriptional activation system was additionally used. A549 cells, the model of NSCLC, transfected with FicG-coding plasmid, induced the maturation of human monocyte derived DCs in co-cultures. Two groups of C57BL6 mice bearing a subcutaneous LLC tumor were injected intratumorally with in vivo-FePEI and FicG plasmids or in vivo-FePEI and phosphate-buffered saline as a control. Four administrations were performed within 1 week. Tumor volumes and animal survival were monitored for 6 weeks.
Results: Plasmid injections delayed the growth of implanted LLC tumors and significantly improved animal survival rates. Histological examination of specific plasmid-injected tumors revealed lymphocyte infiltrates and remarkable necrosis.
Aims: To determine if a similar subset of CD8 T cells are present in asthmatic human airways and if their presence is associated with evidence for asthmatic airway obstruction.

Methods: BAL cells from asthmatics (n=39) and healthy controls (n=28) were stimulated in culture and immuno-stained for CD8, BLT1 and IL-13. The data were correlated to lung function, serum IgE and airway basement membrane (BM) thickness.

Results: Compared to controls, asthmatics showed higher proportion of CD8-positive lymphocytes in BAL fluid (p < 0.001). A significant proportion of these CD8-positive cells expressed BLT1 in both groups. Importantly, the proportion of BLT1-positive CD8 T cells expressing IL-13 was significantly higher in asthmatic airways compared to controls (p < 0.0001). Furthermore, the proportion of IL-13-producing BLT1-positive CD8 T cells negatively correlated with FEV1 (% predicted) values and FEF25-75% values (p < 0.001). Interestingly, a positive correlation was detected between the proportion of these cells and serum IgE levels as well as BM thickness (p < 0.01).

Conclusions: The presence of IL-13-expressing CD8 T cells is present in the airways of asthmatics, and their accumulation correlates with airway obstruction, serum IgE levels and BM thickness, suggesting a pathogenic role for these cells in human asthma.

P3879

In vivo imaging of NF-kB pathway in acute lung inflammation mouse model can predict a pharmacological response

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NF-kB plays a central role in immunity, inflammation, development, cell survival and has been indicated under a number of pathological conditions of lung diseases, including asthma, chronic bronchitis, and chronic obstructive pulmonary disease. In this study, we assessed the in vivo activation of NF-kB signaling in lung tissue using a biosensimaging system (Vivoscope) to monitor activation of an NF-kB promoter in response to lipopolysaccharide stimulation. A plasmid contained responsive elements of NF-kB and luciferase as a reporter gene has been delivered intravenously in nude mice at the concentration of 40 μg per mouse using in vivo-jetPEI™ from Polyplus as a transfectant agent. One week after DNA delivery lungs were harvested, and the lungs imaged using bioluminescence (BLI) at 2, 4, 7 and 24 hs. The ability of the IKK2 inhibitor MLN120B orally administered at the dose of 300 mg/kg to counteract NF-kB activation has been demonstrated (BLI) at 2, 4, 7 and 24 hs. The level of VEGF in the blood correlated with parameters of neoangiogenesis in the lungs tissue (r = 0.37, p = 0.001). Patients with PH in comparison with patients without PH demonstrated higher concentrations of ET-1 and PAI-1 (r = 0.34, p = 0.005 and r = 0.37, p = 0.002 respectively). Invert correlation was established between PAI-1 and Dc0 (r = 0.71, p = 0.05). PAI-1 and FVC (r = 0.72, p < 0.05).

Conclusion: These data demonstrate the important role of the studied markers of ED and neoangiogenesis in the mechanisms of IIP progression and may be used as predictors of survival.

P3882

Increased polysialylation in lung tissue of patients with idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial lung disease of unknown etiology. The disease is characterized by alveolar destruction, uncontrolled fibroblast proliferation and excess matrix production, resulting in progressive dyspnea, a decline in lung function and loss of gas exchange properties. So far, only pirlfimogene has been shown to exert some efficacy in IPF and lung transplantation represents the only option to prevent death. Polysialic acid (polySia) is a developmentally regulated negative charged glycan which is predominantly found in neural tissue and tumors, where polySia is involved in the modulation of cell adhesion and migration processes. Therefore, we asked the extent of polysialylation in IPF (n=22) and donor (n=20) lung tissues obtained during lung transplantation. We observed an up-regulation of the polysialyltransferases ST6SiaI and ST8SiaIV, the key enzymes of polySia biosynthesis, using quantitative real time PCR in IPF patients. In agreement with an increased mRNA expression level of both trans- f erases we detected increased polySia levels in tissue samples of IPF patients in comparison to donor tissue by Western blotting. Using a glycoproteomics approach we were able to identify NCAM as the polySia carrier which could be confirmed by Western blot analysis. Surprisingly, polySia-NCAM was located intracellularly in vesicles of ciliated bronchial epithelial cells as well as Clara cells. However, the role of polySia-NCAM in the bronchoalveolar system and especially during the development and the pathophysiology of IPF needs to be further investigated.

P3883

Human neutrophil peptides as biomarkers for monitoring respiratory functional impairment in sarcoidosis

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Background: Human Neutrophil Peptides (HNP) are cationic peptides with a...
The pathogenesis of lung disease in cystic fibrosis (CF) has not been fully elucidated, however, neutrophil-dominated inflammation is thought to play a major role. Nonetheless, a number of proteases produced by other cells in the lung may play a pivotal role. Furthermore, host defense proteins such as SLPI, β-defensins and lactoferrin play a role for cathepsin S in the diminution of the lung antiprotease and antimicrobial screen possibly leading to lung destruction and favouring conditions for bacterial infection. We have identified epithelial cells as a source of cathepsin S in the CF lung with the demonstration that CF bronchial and tracheal epithelial cell lines express and secrete significantly more active cathepsin S than normal cells in the absence of proinflammatory stimulation. These findings were confirmed in primary human bronchial epithelial cells from CF patients. On the basis of our results to date, we postulate that upregulated cathepsin S plays an important role in CF lung disease. Human lysosomal cysteine proteases are a family of proteases that have been relatively unexplored in the area of CF lung disease. We have shown that cathepsin S activity is increased in CF bronchoalveolar lavage fluid. In addition to lung tissue degradation, cathepsins have been found to play a role in the destruction of host defence proteins such as SLPI, β-defensins and lactoferrin. These findings indicate a role for cathepsin S in the diminution of the lung antiprotease and antimicrobial screen possibly leading to lung destruction and favoring conditions for bacterial infection. We have identified epithelial cells as a source of cathepsin S in the CF lung with the demonstration that CF bronchial and tracheal epithelial cell lines express and secrete significantly more active cathepsin S than normal cells in the absence of proinflammatory stimulation. These findings were confirmed in primary human bronchial epithelial cells from CF patients. On the basis of our results to date, we postulate that upregulated cathepsin S plays an important role in CF lung disease and we are currently investigating reasons for this upregulation of cathepsin S in CF epithelial cells. This data will shed light on the role of cathepsin S in CF; an area that has been overshadowed to date, and may open up new avenues for exploration in the search for an effective therapeutic target in CF lung disease.
Establishment of reference values for differential cell counts in nasal lavage of healthy young adults.

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Background: Upper airway inflammation could be reflected by nasal lavage cytology, which is characterized by advantages of non-invasive, simple, objective and costless. However, reference values nasal lavage cytology was not established.

Objectives: To establish reference values and positive standard for nasal lavage cytology through screening normal healthy subjects and patients with allergic rhinitis according to strict inclusion criteria.

Methods: 43 normal healthy volunteers (control) and 166 subjects with allergic rhinitis (AR) were enrolled after detailed history inquiry, physical examination and allergen skin prick test. Nasal lavage cytology tests were performed, and the standard for judgment was defined as the average count of different inflammatory cells per 20 fields under 200× microscopic view.

Results: There was no statistical significance in gender, age, height and weight among each group. 95% CI of neutrophils, eosinophils, and lymphocytes were (0~0.65)/×200 and (0~1.70)/×200, respectively. The median (interquartile range) of neutrophils were 0.65/×200 in AR group, which showed no statistical difference (P>0.05) with that of normal group (0/×200). A significant difference was found in the median (interquartile range) of eosinophils [0.60 (2.24/×200)] in AR group as compared with that of normal control group (0/×200). P=0.001.

Conclusions: Establishment of reference values of nasal lavage cytology test is helpful to discriminate normal individuals and patients with allergic rhinitis, but also a new tool for objective reflection on upper airway inflammation, which is of great value for scientific and clinical purposes.

The dietary antioxidant quercetin boosts pulmonary antioxidant defenses

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We have demonstrated that single oral supplementation of the dietary antioxidant quercetin reduces oxidative stress in sarcoidosis patients. Apart from its direct oxidant scavenging properties, quercetin has also been suggested to boost endogenous antioxidant defenses indirectly by activation of redox sensitive signaling pathways. Therefore, we investigated the effect of orally applied quercetin on pulmonary redox balance.

C57BL/6J mice were sacrificed 3 or 16 hours after receiving an oral quercetin bolus (6 mg/animal). Total antioxidant capacity, quercetin concentration and the expression of nuclear factor erythroid derived (Nrf2)-regulated antioxidant genes were evaluated. The possible influence of Nrf2 was also explored in vitro by treating quercetin-preloaded BEAS-2B human bronchial epithelial cells with the pro-oxidative agent bleomycin.

Total quercetin concentrations in plasma and lung tissue displayed a rapid but transient increase, which was associated with enhanced total antioxidant capacity. After 16 hours, amplified pulmonary mRNA levels of various antioxidant genes including catalase, superoxide dismutase, heme oxygenase 1 and -glutamyl cysteine synthetase were observed. Additionally, oral quercetin administration increased Nrf2 gene expression. In the BEAS-2B cells, quercetin also activated Nrf2 and interestingly, this induction was augmented by bleomycin. Moreover, quercetin pre-treatment inhibited bleomycin-induced ROS production.

In conclusion, our results indicate that oral quercetin may exert beneficial effects by boosting pulmonary antioxidant defenses and suggest a possible involvement of Nrf2 herein. The therapeutic value of our findings is currently explored in a murine fibrosis model.

Clinical evaluation of angiogenesis and coagulation in pulmonary sarcoidosis

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The aim of our study was to evaluate the influence on prognosis of patients with pulmonary sarcoidosis of some mediators autonomous angiogenesis and activation of coagulation (vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1).

Patients and methods: 46 patients with morphologically proved pulmonary sarcoidosis were examined. Standard clinical examination, pulmonary function testing, 6-min walk test (6 MWT), echocardiography, high-resolution CT (HRCT) were evaluated. Plasma concentrations and expression in lung biopsies of VEGF and PAI-1 were evaluated by immunoassay (ELISA) and immunohistochemistry. Monochrometry of lung vessels were performed.

Results: 12/26% patients presented pulmonary hypertension (p<0.05). Plasma concentrations of PAI-1 and VEGF correlated positively with HRCT patterns of fibrosis in lung (r=0.38, p<0.006 and r=0.37, p=0.002 respectively) and were more high in patients with PH in comparing to patients without PH (P=1.206, 15.1-27.2/nM/l vs 14, 9.1-18.2/nM/l, p=0.001 respectively and VEGF: 42.7±31.6, 1-55.4/2/mL vs 28.01, 180-3(0.06, Hr/mL, p=0.001 respectively). VEGF expression in lung tissue correlated positively with morphology of pulmonary vasculitis (r=0.34, p=0.001). HRTC hockycomb patterns (r=0.45, p=0.002).

Conclusion: Degree of alterations of the coagulation system and angiogenesis may be discussed as survival prognostic markers for pulmonary sarcoidosis.

Detection of serum anti-endothelial cell antibodies (AECA) in COPD rats

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Background: Chronic obstructive pulmonary disease (COPD) may be a systemic inflammatory disease. Autoimmunity abnormalities and a potential role of COPD includes micro-vascular destruction. Anti-endothelial cell antibodies (AECA) are a type of circulating antibodies which bind to endothelial antigens and induce endothelial cell damage. It is unclear whether the AECA play a role in COPD mechanisms.

Objective: To detect the serum level of anti-endothelial cell antibody in adult rats of COPD in order to investigate the significance of AECA in COPD mechanism.

Methods: Replicated COPD rat models with passive-smoking and lipopolysaccharide (LPS) induce traheas injections. Anti-endothelial cell antibodies (AECA) of rats were examined by ELISA.

Results: In smoking rats with simple airway inflammation, the alveolar septum thickened but was not destroyed, AECA1 49.4±8.7 ng/L. COPD rats had airway inflammation and emphysema. AECA1 138.46±7.85 ng/L. Compared with the normal control group (62.89±10.68 ng/L), AECA levels in the two test groups were much higher.

Conclusion: Autoimmune constituents which induce endothelial cell lesions may participate in the pathogenesis of COPD; detection of serum AECA levels in COPD may have some clinical significance.

The pathogenesis of COPD

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Background: Chronic obstructive lung diseases (COPD) are the major cause of death and disability worldwide. The major risk factor for COPD is tobacco smoke. Cell adhesion molecule CD146 is expressed in all types of human endothelial cell (EC) and exists in a membrane-anchored and a soluble form (sCD146). The plasma concentration of sCD146 is modulated in inflammatory diseases associated with endothelial alterations.

Aim and objectives: To investigate the role of endothelial CD146 in the pathogenesis of cigarette smoke (CS)-induced emphysema.

Methods: Sprague Dawley rats were exposed to second hand CS for two months. The lung tissue and bronchoalveolar lavage (BAL) cells were examined for CD146 gene and protein expression and emphysema development as measured by M/L scID146 levels were determined in circulation and BAL fluid in rats and in patients with COPD. CD146 expression and function was also examined in rat pulmonary EC exposed to CS in vitro.

Results: Sprague Dawley rats exposed to cigarette smoke for 2 months developed significant emphysematous changes (as measured by mean linear intercept) and had increased levels of circulating and bronchoalveolar lavage fluid sCD146. Treatment of rat pulmonary EC with cigarette smoke extract in vitro also resulted in a decreased membrane-bound CD146 expression and increased sCD146 levels in the medium. Moreover, circulating levels of sCD146 were significantly increased in serum of COPD patients and correlated with the disease severity.

Conclusion: Our data indicate that CD146 is involved in CS-induced vascular dysfunction and that CD146 can be a candidate marker for COPD/ emphysema.

Effects of steroids on inflammatory cell number and function in the proximal and distal airways

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Introduction: Steroids are often prescribed for patients with mild/moderate COPD but is not clear how these commonly prescribed drugs affect inflammatory cell numbers/function in the proximal and distal airways.

Methods: Matched proximal and distal airways tissue was obtained from 37 patients. Fourteen patients had no evidence of airways obstruction (FEV1/ FVC>0.76±0.01) and 23 had evidence of mild/moderate COPD (FEV1/ FVC<0.58±0.02). Eleven of these patients were prescribed steroids at the time of surgery.
Novel mechanisms in lung injury

410. Novel mechanisms in lung injury

P3894
Nitrosative and cytokine status in patients with COPD and chronic cor pulmonale (CCVD)

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The aim of the study was to investigate the dynamics of nitric oxide (NO) stable metabolites concentration in exhaled breath condensate (EBC) as markers of the nitrosative stress and circulating inflammatory cytokines in COPD and CCVD. Material and methods: 50 males inpatients were enrolled in the study (age = 51.67 yrs.). All patients were divided in two groups: group 1 contains 23 patients with COPD exacerbation only. The control group consisted of 21 healthy volunteers. The investigation was performed only. The control group consisted of 21 healthy volunteers. The investigation was performed by ELISA. Results: The TNN levels in EBC as well as in blood plasma were significantly higher than the COPD cases admitted with acute attack or respiratory failure. The TNN concentration was measured using the spectrophotometric method; 3-NT and cytokines (TNF-α, IL-8) concentrations in blood plasma were investigated with specific enzyme immunoassay. Conclusion: The results obtained demonstrate the increase of nitrosative/ cytokines stress parameters as a systemic reaction in patients with COPD and CCVD compared with COPD patients only.

P3895
Leptin modulates host defense against chronic cigarette smoke inhalation in mice

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Rationale: Several hallmarks of COPD, including pulmonary and systemic inflammation, can be mimicked in mice by cigarette smoke (CS) exposure. We recently found increased expression of the pleiotropic adipokine leptin by resident lung cells in smokers and patients with COPD versus never-smokers. To unravel the involvement of leptin in COPD pathogenesis, innate and adaptive immune cell recruitment and remodelling upon chronic CS exposure was evaluated in leptin-receptor deficient db/db mice. Methods: WT C57/BKS and db/db mice were exposed to air or CS for 16 weeks (4 exposures/5, 5 wk). At 24h after the final exposure, bronchoalveolar lavage fluid (BALF) and lung tissue were processed to examine pulmonary inflammation and remodelling. Results: The role for autoimmunity in the pathogenesis of COPD is controversial, and the identity of putative autoantigens is subject to debate. In order to examine the role for autoantibodies in COPD, we cloned the complete variable light and heavy chains from single-cell sorted IgG or IgA-positive activated memory B cells isolated from COPD and control lung tissue, and expressed these as complete human Ig mononclonal antibodies (HumAbs). These HumAbs were tested for autoactivity by histology using lung tissue sections of COPD patients and healthy controls and lung cell lines. In addition, serum of COPD patients and never-smokers was used to determine binding of antibodies to epithelial, fibroblast, and endothelial cell lines. The HumAbs stained multiple cells and structures in lung tissue sections such as smooth muscles cells, epithelial cells, and the adventitia. The cell lines examined thus far, two epithelial cell lines, were also stained by the HumAbs. The results from these in vitro studies illustrate the complexity of autoactivity in COPD in concomitantly with the preferential binding of different types of lung cells by antibodies in serum of COPD patients, individual antibodies may also target multiple cells and structures in the lung.

P3896
Paraosinace activity in patients with COPD

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Aim: Oxidant/antioxidant disequilibrium is an important problem in pathogenesis of COPD. This disequilibrium is effective in development and progression of COPD. The increased oxidative stress in COPD is not only associated with rise of oxidants but also with the decrease of antioxidant capacity. Paraoxazone 1 (PON1) functions as one of the endogenous free radical scavenging system in human body. PON1 is localized in clara cells, endotel cells and type 1 pneumocytes of the lungs. In this study we aimed to study the PON1 activity in COPD patients with stable condition, had acute attack and developed respiratory failure. Material and methods: Twenty five patients with stable COPD (group1) (mean age 62.9±9.4), 25 cases with acute COPD attack (group2) (mean age 63.8±9.0), 25 patients with hypercapnic respiratory failure (group3) (mean age 65.6±12.9) and 25 healthy individuals for control group (mean age 34.8±9.8), totally 100 cases, were enrolled to the study. All cases enrolled to the study underwent routine biochemical analysis including PON1 activity and lipid profile. Results: There was significant difference between groups with respect to PON1 levels (p<0.0001). PON1 activities of COPD patient groups (group 1=96,5±87,4U/L, group 2=51,4±32,8U/L, group 3=47,1±27,5U/L) were lower than control group (185,4±110,1U/L, p<0.0001). Also PON1 activity of stable COPD patients was higher than the COPD cases admitted with acute attack or respiratory failure (group2 and 3) (p<0.05). Conclusion: This findings show that PON1 activity may have a role in COPD pathogenesis and endogen antioxidants might be depleted by increased oxidative stress in COPD. This also advocates that oxidative stress may have a role in acute COPD attacks.
P3908 Bronchial antiproteases activation as a tolerance factor to COPD development in healthy long term smokers
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Not all smokers suffer from COPD. It is possible that tolerance to COPD emergence among healthy long term smokers is supported by suppressing the excessive proteolytic activity.

Aim: To investigate the factors of tolerance to COPD development among healthy long term smokers according to content of proteases and antiproteases in induced sputum.

Methods: There are 145 stable COPD patients and 48 long term smoking men (>30 pack/year), without symptoms of COPD have been enrolled in our research.

The control group consisted of 48 healthy nonsmokers volunteers. All patients were men of identical age of 59.2±4.07 years. Induced sputum was studied on elastase, protease’s inhibitor α1, macroglobulin α1.

Results: An activity of protease’s inhibitor α1 and macroglobulin α1 in induced sputum of long term smokers is higher than among healthy non-smokers and patients with COPD.

The activity of proteases and antiproteases in induced sputum

<table>
<thead>
<tr>
<th>Groups and stage COPD</th>
<th>Protease’s inhibitor α1</th>
<th>Macroglobulin α1</th>
<th>Elastase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy non-smokers</td>
<td>148.45±6.912</td>
<td>166.5±3.862</td>
<td>0.56±0.0012</td>
</tr>
<tr>
<td>Healthy long-term smokers</td>
<td>181.47±1.777</td>
<td>76.1±4.84</td>
<td>0.62±0.001</td>
</tr>
<tr>
<td>COPD II</td>
<td>95.02±6.70</td>
<td>14.0±0.36</td>
<td>1.62±0.70</td>
</tr>
<tr>
<td>COPD III</td>
<td>62.2±7.6</td>
<td>17.0±2.61</td>
<td>3.18±0.30</td>
</tr>
<tr>
<td>COPD IV</td>
<td>54.5±6.33</td>
<td>15.3±0.76</td>
<td>5.68±0.29</td>
</tr>
</tbody>
</table>

Conclusions: The tolerance to development COPD among long term smokers is supported high activity of antiproteases in bronchial region.

P3909 Model of staged development chronic obstructive pulmonary disease (COPD) in rats
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Models of COPD open ways of studying pathogenesis, searching for therapeutic targets and new health care trends.

Aims: To reproduce the successive stages of COPD in experiment.

Methods: Model of COPD was induced in Wistar rats by long-time intermittent nitrogen dioxide (NO2) inhalation (15 ppm, 1,5 h/day for 60 days). Histological specimens were stained with hematoxylin-eosin. CD3 expression in bronchial walls and interstitium was determined by immunohistochemistry. TNFα and TGFβ1 were determined in serum and bronchoalveolar lavage fluid (BALF).

Results: After 15-day NO2 exposure acute response to injury was observed: epithelium desquamation and focal proliferation, swelling of submucosa, bronchial gland degeneration, lung tissue hyperextension were revealed. After 30 days cell infiltration of submucosa and hyperplasia of goblet cells were added. After 60-day exposure squamous metaplasia of ciliated epithelium, muscle plate atrophy, focal sclerosis, emphysema were identified. At this stage increase of CD3 expression was revealed in walls of bronchi and interstitium that indicated the presence of large number of T-lymphocytes (6.1±±1.59 vs. 28±±1.23 in control rats, p <0.05). TNFα increased in serum (125.94±16.21 vs. 60.±6±6.34 pg/ml in control, p <0.05) and BALF (204.9±25.76 vs. 15±±0.03 pg/ml in control, p <0.05). TGFβ1 increased in serum 18-fold and in BALF – 8-fold from control (p <0.05).

Conclusion: The model allows to reproduce stages of COPD from acute inflammation to lung tissue remodeling (emphysema and focal fibrosis). The model adequacy is confirmed by COPD symptoms: increased expression of CD3-lymphocytes in bronchial walls and lung parenchyma, multiple increased TNFα and growth factor TGFβ1.

P3910 Lipoxin A4 receptor expression in smokers with and without COPD
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1Department of Experimental Pulmonology and Pathomorphology, Research Institute of Pulmonology, St. Petersburg, Russian Federation; 2Department of Pulmonology, St. Petersburg, Russian Federation

Background: The lipoxin A4 receptor, LXA4R/FPR1-L, is a G protein-coupled receptor LXA4R with high affinity binds anti-inflammatory lipoxin LXA4 and with low affinity - N-formylated proinflammatory peptides. The aim of our study was to evaluate FPR1 expression in nonsmokers, asymptomatic smokers and in patients with COPD.

Patients and methods: 6 nonsmokers, 7 asymptomatic smokers and 5 moderate COPD patients undergoing lung resection for a solitary peripheral non-small cell carcinoma were enrolled in the study. Immunohistochemical methods were used to evaluate FPR1 expression in airways and alveolar walls.

Results: FPR1-1 expression was observed in airways epithelial cells, macrophages, lymphocytes and neutrophils. Obtained results showed that asymptomatic smokers had increased numbers of FPR1-1 positive cells in alveolar walls compared to nonsmokers (157±±59 vs. 38±±13 cells/mm², p <0.002). At contrast, COPD patients had decreased numbers of FPR1-1 positive cells compared to asymptomatic smokers (23±±7 vs 157±±59 cells/mm², p <0.002). In addition, COPD patients had a tendency of decreased FPR1-1 expression compared to nonsmokers. When all smokers were analyzed together, a significant positive correlation was found between the number of FPR1 positive cells and airflow obstruction, FEV1% (Rho±±0.66, p=0.02).

Conclusion: Downregulated FPR1-1 in COPD patients may explain persistence of inflammatory process in alveolar area in COPD, whereas upregulation in asymptomatic smokers could serve as adaptive mechanism limiting inflammatory process.

P3911 Lung injury and apoptosis in COPD: Effect of a recombinant anti-protease derived from trappin-2
Annabelle Tanga, Ahlame Saidi, Sandrine Dallet-Choisy, Marie-Louise Zani, Thierry Moreau.

Introduction: In chronic obstructive pulmonary disease (COPD) it is well established that neutrophil serine proteases' elastase (HNE), protease 3 (Pr3), cathepsin G (CG) contribute to lung injury. In order to target these proteases in COPD, we previously developed an anti-protease derived from trappin-2 modified to inhibit the three proteases at the same time. The goal of the study is to evaluate the protective effect of this inhibitor (trappin-2.62L) against the degradation of lung epithelium and apoptosis of epithelial cells induced by proteases.

Methods: Alveolar epithelial cells (A549) cells were exposed to serine proteases in presence or absence of trappin-2.62L (T2A62L) with various concentrations and experimental conditions. The protective effects of T2A62L towards proteolytic damages were estimated by observation of changes in cell morphology and by the measurement of the cellular detachment. The protective effect of T2A62L towards A549 apoptosis induced by proteases was evaluated by flow cytometry.

Results: Serine protease induce cell morphological changes, cellular detachment (58.78, 85.35% for HNE, Pr3, CG respectively) and apoptosis of epithelial cells (5 and 2 fold increases with HNE and Pr3). Addition of T2A62L diminishes the proteolytic damages (5,10, 35% for HNE, Pr3, CG) and reduces significantly the rate of apoptotic cells.

Conclusion: The approach using a cellular model demonstrate that T2A62L exerts anti-proteolytic and a protective effect towards apoptosis induced by serine neutrophil proteases. So, these results confirm the therapeutic potential of this inhibitor for treatment in COPD.

P3912 Effect of phototherapy in phospholipids' composition of membranes of lymphocytes in experimental COPD
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Ministry of Health of the Republic of Uzbekistan, Republican Specialized Scientific-Practical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan

Introduction: Membrane phospholipids (PL) provide functional integrity of the cells of respiratory tract.

Aim: To study membrane phospholipids' composition of peripheral blood lymphocytes in the dynamics of phototherapy in rats with experimental COPD.

Methods: An experimental COPD was reproduced in 60 white rats under the influence of tobacco smoke. For half of them we used the method of phototherapy of concentrated pulsed light (CPL) at wavelengths from 600 to 800 nm. Phototherapy was carried out daily for 10 days. The control group consisted of 10 healthy rats. To study the phospholipids' fractions of lymphocytes we used the high-flow horizontal chromatography.

Results: In rats with experimental COPD, compared with the control group, phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were reduced by 31.8% (P <0.01) and 43% (P <0.01), the content of lysophosphatidylcholine (LPC) and lysophosphatidylethanolamine (LPE) was increased two-fold (P <0.01). Free fatty acids (FFA), compared with the control, increased by 47.2% (P <0.01) with a decrease in total phospholipids (TPL) by 17% (P <0.01). After 10 sessions of phototherapy we defined increase in PC and PE by 18.8% and 28.4% compared with the group of COPD without treatment, and this was accompanied by a decrease in LPC and LPE by 35.1% and 40.9% (P <0.05 in all cases). Tendency to normalization of FFA and TPL had no statistical significance.

Conclusion: Experimental COPD in the rats is accompanied by quantitative changes in the main fractions of phospholipids in the membranes of peripheral blood lymphocytes. Conducting a course of phototherapy by CPL contributes to positive changes in membrane phospholipids of the lymphocytes.
(Background) 25-Hydroxycholesterol (25-HC) is produced from cholesterol by cholesterol 25-hydroxylase and is related to atherosclerosis in vessels. Recently, 25-HC production was enhanced in the airways of COPD patients compared to healthy subjects. Cholesterol 25-hydroxylase was localized in alveolarmacrophages and pneumocytes in COPD. The amounts of 25-HC in the sputum were significantly increased in COPD patients and the degree of 25-HC production was negatively correlated with the lung function. The amounts of 25-HC in the sputum had significant positive correlations with the interleukin-8 (IL-8) levels and neutrophil counts in the sputum. Treatment with 25-HC augmented neutrophil accumulation in the airways and the production of chemokines in mice. 

(Conclusions) 25-HC production was enhanced in the airways of COPD patients and could cause neutrophilic inflammation.

(P3904) Time course analysis of lung function and morphometric parameters in a murine model of emphysema
Clarice Olivo, Bruna Scarpa, Francine Almeida, Petra Arantes, Fernanda Lopes, Milton Martins. Department of Medicine, Universidade de São Paulo, São Paulo, Brazil

Proteolytic enzymes have been used to induce emphysema in rodents to study mechanisms of this disease pathogenesis. However, few studies have evaluated the time course of the development of pulmonary emphysema after nasal instillation of elastase.

Objectives: To describe the progression of emphysema after porcine pancreatic elastase (PPE) nasal instillation in mice.

Methods: 64 adult male Balb/c mice received either a nasal drop of 50 μl (0.667 UI) of PPE (PPE) or saline (S) and were studied on days 1, 7, 14 and 21 after PPE instillation. For each time, we analyze airway resistance (RAW), tissue elastin (Gtis) and tissue elastance (Htis). Inflammatory profile was performed after PPE instillation. For each time, we analyzed airway resistance (RAW), tissue elastin (Gtis) and tissue elastance (Htis). Inflammatory profile was performed after PPE instillation.

Results: There was an increase in inflammatory cells in PPE groups since the 1st day, characterized by an increase number of neutrophils and macrophages which remained until the 21th day. However the increase in lymphocytes became evident only at 7th day. We observed a decrease in Htis at 7th and 21th days while there was an increase in Gtis at the 1st day and a decrease at the 21th day. We did not observe any differences for RAW values. The increase in Lm was observed in PPE group since the 1st day and was maintained throughout different times.

Conclusions: In this experimental model we observed an earlier inflammatory process concomitant with alveolar enlargement, suggesting that protease-antiprotease imbalance influence the development of emphysema. Supported by FAPESP, LIMHC-FMUSP, CNPq, Brazil

(P3905) Effects of cancer cachexia on the alveolar morphology of the mouse lung
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Cancer cachexia is a complex syndrome with a significant reduction of body weight and a variety of systemic symptoms including respiratory dysfunction. In rodents, calorie restriction causes loss of alveolar surface area, the so-called nutritional emphysema. We hypothesized that alveolar alterations and loss of gas exchange surface area are present in the cancer-cachetic mouse. C57Bl6 mice were randomly assigned to subcutaneous injection of Lewis lung carcinoma cells (tumor group, TG) or saline injection (control group, CG). Mice were sacrificed 21 days later and lungs were processed for light and electron microscopy. Cancer cachexia did not differ between groups the volume of lamellar bodies per unit alveolar surface area was significantly reduced in TG (TG: 25.3±3.7 mm2/m2; CG: 40.2±13.5 mm2/m2; p<0.05). Quantitative expression of surfactant proteins A, B, C and D was not different between CG and TG as shown by RT-PCR.

In summary, despite a reduced ratio between the volume of the intracellular surfactant pool and the alveolar surface area in TG, there was no evidence for a significant disturbance of the gas exchange region due to cancer cachexia. In particular, weight loss was not associated with loss of alveolar surface area.

Conclusions: Short term aerobic training seems do not decrease features of pulmonary allergic disease in mice.
P3907
Contribution of TGFβ1 and TIMP2 to clinical activity of asthma and COPD
Navid Abofzafkh Zade Ghalejoghi 1, Mostafa Ghaneli 1, Mohammad Reza Norouzi 2, Ali Amiri Harandi 2, Abbas Ali Imami Fooladi 1,2
1Research Center of Chemical Injuries, Buqiyatulllah University of Medical Sciences, Tehran, Islamic Republic of Iran; 2Research Centers of Molecular Biology, Buqiyatulllah University of Medical Sciences, Tehran, Islamic Republic of Iran

Introduction: The process of bronchial tissue repair and remodeling in airway diseases depends on balance between production and degradation of different cytokines, leading to the regulation of extracellular matrix turnover finally.

Objectives: This study was designed to evaluate contribution of Transforming Growth Factor β1 (TGFβ1) and Tissue Inhibitor of Metalloproteinase-2 (TIMP2) to clinical activity and reversibility of asthma and chronic obstructive pulmonary disease (COPD).

Methods: In a cross-sectional study on two groups of 29 asthmatics (14 males and 15 females) and 13 male COPD patients, we evaluated TIMP2 and TGFβ1 expression using semi-quantitative PCR on induced sputum samples. The relation among TIMP2 and TGFβ1 and pulmonary function test (PFT) indices and disease free period was assessed.

Results: Higher pulmonary function test (PFT) indices and longer disease free period was seen in COPD patients with raised expression of both TGFβ1 and TIMP2. On the other hand asthmatic patients had better pulmonary function status with raised TIMP2 and decreased TGFβ1 expression (p<0.05).

Conclusion: It seems that different effect of cytokines like TGFβ1 and TIMP2 in both diseases is depended on underlying inflammatory process in airways epithelium. We supposed that TGFβ1 bidirectionally affects activity of disease in asthma and COPD. Furthermore TGFβ1 as a biomarker in sputum may have a role for evidence-based drug prescribing like corticosteroids in patients with COPD and asthma.

P3908
The role of cathepsin D, H & K in the regulation of tumstatin levels in asthmatic airways
Janette Burgess 1,2,3, Karryn Grafton 1,2,3, Gavin Tjin 1,2, Josephine Middelburg 1,4
1Pharmacology, The University of Sydney, Sydney, NSW, Australia; 2Cell and Molecular Biology, Woolcock Institute of Medical Research, Sydney, NSW, Australia; 3Pharmacology, The University of Sydney, Sydney, NSW, Australia; 4Airway Remodelling, Cooperative Research Centre for Asthma and Airways, Sydney, NSW, Australia

Introduction: Angiogenesis is a prominent feature of remodelling in asthma. We previously reported that tumstatin, an endogenous angiogenic inhibitor which is the non-collagenous domain-1 (NC1) of the collagen IV α3 chain is absent from asthmatic airways. Tumstatin is released from the basement membrane by specific proteases. Cathepsins D, H and K (members of a broad family of proteases that degrade ECM proteins including collagen IV in other organs) are increased in inflammatory diseases and modulate tumour angiogenesis. We hypothesised that cathepsin D, H and/or K plays a role in the absence of tumstatin in asthmatic airways.

Methods: Cathepsin mRNA expression was measured by real time RT-PCR. Immunohistochemistry was used to measure cathepsin D, H and K in human airway tissue sections. Recombinant tumstatin and airway tissue sections were digested with active recombinant cathepsin D, H and K and the resultant cleavage products analysed by polyacrylamide gel electrophoresis. 

Results: Human airway smooth muscle cells express cathepsin D and H mRNA. In both asthmatic and nonasthmatic airway sections inflammatory cells exhibit strong staining for cathepsin D. Cathepsin H and K are also strongly expressed in asthmatic airway tissues. Recombinant tumstatin was completely degraded by recombinant cathepsin D and H whilst cathepsin K degradation produced a 10kDa cleavage product. In human tissue sections recombinant cathepsin D completely digested tumstatin. Digestion with cathepsin K resulted in greater detection of the tumstatin antigen.

Conclusion: These findings suggest that cathepsin D, H and K may play a role in the regulation of tumstatin levels in the asthmatic airways.

P3909
Inhibitory profiles of alpha-1-antitrypsin from PiZ & PiSZ individuals and implications for tissue destruction in emphysema
Nicola Sindel 1, Timothy Dalton 1, Robert Stockley 1,1 ADEPT Project, Lang Function and Sleep Department, University Hospital Birmingham, Birmingham, West Midlands, United Kingdom; 2School of Biosciences, University of Birmingham, Birmingham, United Kingdom

Introduction: Neutrophil elastase (NE) causes emphysema in animal models. Heterozygote (Z) deficiency of its inhibitor alpha-1-antitrypsin (AAT) is associated with human emphysema. The role of heterozygote deficiency (SZ) is unclear.

Aims: To compare the inhibitory profiles of equimolar amounts of AAT from Z & SZ serum with pure AAT & M serum. The hypothesis is that Z AAT inhibits NE less efficiently than SZ & M.

Methods: AAT concentration was measured in serum from Z, SZ, M & patients. Increasing amounts of AAT were added to a fixed amount of NE. Residual NE activity was measured spectrophotometrically using both a chromogenic substrate and elastin. This was repeated with pure AAT & alpha-2-macroglobulin (A2M). Results: With a low molecular weight chromogenic substrate, M serum A2M was increasingly inhibited NE as the inhibitor:enzyme molar ratio increased to 1:1. Beyond 1:1 inhibition 15% residual NE activity remained, but not for pure AAT. For SZ serum residual activity was 60%. For Z serum and pure A2M enhanced NE activity was seen as inhibitor:enzyme ratio increased.

With elastin, inhibitory profiles of M, SZ & Z serum were similar to each other. Conclusion: Enhanced NE activity with Z serum likely represents binding to A2M. Deficiency of AAT means that NE is more likely to bind to A2M. A2M NE complexes retain proteolytic potential. These data may have implications for tissue destruction in emphysema.

P3910
Acute effects of an aerobic exercise session on airway inflammation in a murine asthma model
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Background: Chronic effects of aerobic training (AT) seem to decrease inflammation in experimental asthma.

TUESDAY, SEPTEMBER 27TH 2011
Objective: Investigate the effects of a unique exercise session of aerobic exercise in a murine asthma model.

Methods: Male BALB/c mice were divided in 4 groups: Control, AT, ovalbumin sensitized (OVA) and OVA+AT. OVA sensitization groups received: p i.days (0.14;28) and OVA inhaled exposition (OVA%, 3xweek/30min) after the 21st day. In the 28th day animals from AT and OVA+AT groups performed a session of treadmill running for 1 hour (59% maximal intensity). Evaluations: In vivo respiratory mechanic (Flexivent), different cell count in the BALF, and collagen fibers depositions and smooth muscle thickness in the airways were evaluated by an expert.

Results: Initial physical capacity was similar among groups (p>0.05). BALF total and inflammatory cells, collagen fiber and the smooth muscle thickness were increased in sensitized groups (p<0.05). Parameters of respiratory mechanic (Gis and This) were also increased in groups sensitized groups (OVA and OVA+AT; p<0.05).

Conclusions: Aerobic exercise when performed for acutely does not decrease features of experimental asthma such as cell migration, airway remodeling and respiratory mechanic.

P3911

High doses of N-acetylcysteine alone or in combination with inhaled corticosteroids and oxidative stress in patients with COPD

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Background: Oxidant/antioxidant interactions are known to be important process of the pathogenesis of COPD. We aimed to evaluate the effects of 6-month oral N-acetylcysteine (NAC) treatment 600 mg twice daily alone or in combination with inhaled corticosteroids (ICS) on reactive oxygen species (ROS) production by granulocytes in peripheral blood measured by luminol-dependent chemiluminescence and its effect on pulmonary lipid peroxidation by malondialdehyde (MDA) level measurement.

Methods: 62 patients with stable COPD (36 males, mean age 66.8±7.5 years, GOLD stage I-IV) were divided into two treatment groups. Group 1 received bronchodilators as basal treatment and NAC. Group 2 received NAC plus ICS in addition to basal treatment. Clinical examination, pulmonary function tests and blood collection were performed at baseline (T0) and repeated after 1 (T1), 3 (T3) and 6 months (T6) of treatment.

Results: Spontaneous ROS generation had trend to decrease at T3 in both groups, and achieved significant difference at T6 only in group 2 (p=0.004). At the same time, impaired ROS generation did not significantly change in both groups (p>0.05). Antiperoxide serum activity was increased from T0 to T1 however further levels did not substantially changed. We registered MDA plasma level decrease in both groups during all treatment period, but significant difference from T0 to T6 was observed just in group 2 (1.8 μmol/L vs 1.4 μmol/L; p=0.017).

Conclusion: We conclude that combination of oral NAC 1200 mg/day with ICS for 6 months reduces the oxidant burden in airways of stable COPD patients and achieved significant difference at T6 only in group 2.

P3912

Ceruloplasmin efficacy in patients with asthma exacerbations

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Ceruloplasmin (C) proves to be a valuable preparation in the treatment of patients with Ba exacerbations. The obtained data suggested the suppression of lipid peroxidation and damaging effect of airway cooling under inhaled glucocorticosteroids influence.

411. Obstructive sleep apnoea: clinical aspects II

P3914

Autonomic cardiac modulation response due to the use of an oral appliance to treat OSA – Pilot study

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Introduction: Obstructive sleep apnea (OSA) alters autonomic variability during sleep and wakefulness. Little has been shown about the possibility of achieving the cardiac balance during a mandibular repossession appliance (MRA).

Objective: To evaluate the effect of MRA to treat OSA on heart rate variability (HRV) prior and after 6 month of the device usage.

Methods: Eight OSA patients with moderate obstructive apnea were enrolled in this study. Patients reported snoring, nocturnal breathing arrests, tiredness upon awakening and difficulty in concentrating. The inclusion criteria was present at least a 7.0mm maximum protrusion, 40mm of mandibular opening, 8-10 teeth in each arch, posterior dental health. Treatment consisted of continuous use of the oral appliance during approx. 6 months. Polysomnography and HRV analysis were performed before and after the treatment.

Results: The AHIl was reduced from 45.6±4.90 to 10.0±2.7 (p<0.05), the mean SaO2 nadir increased from 73.3±10 to 88.0±4.5 (P<0.05) and REM% increased from 18.6±4.6 to 22.0±3.4 (p<0.05), the sleep stages1,2,3 and sleep efficiency showed no statistical significance. The frequency-domain parameter were significant for both Fast Fourier Transform and Wavelet spectral method only in parasympathetic area, which improved from 197.0±70.0 to 105.3±43.0 (p<0.05) and from 221.0±85.0 to 102.0±33.0 respectively (p<0.05). The RR interval improved from 776.0±54.0 to 792.0±45.0 but was not significant.

Conclusion: The oral appliance used in this work was effective in respiratory events and tended to improvement of cardiac autonomic modulation, as reflected by changes in heart rate variability. Further evaluation with a larger sample is needed.

P3915

Evaluation of the relations between the obstructive sleep apnea syndrome and obesity by standard antropometric obesity indexes

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Introduction: Obesity is an important risk factor in the development of obstructive sleep apnea syndrome (OSAS).

710s
Aims and objectives: To investigate whether the general body adiposity or local lipodissosis was a risk factor in the evolution of OSAS by examining the relationships between the anthropometric obesity indices such as waist (WC) and neck circumference (NC), body mass index (BMI) and OSAS in Turkish adult population, and to access the possible differences by gender. Methods: The records of 499 subjects were examined retrospectively. The data related to polysomnographic, demographic and anthropometric indexes of the subjects were recorded. The patients whose apnea-hypopnea index were ≥ 5 was determined as OSAS group. Results: Of the subjects who underwent polysomnography: 431 (86.37%) were OSAS. The average BMI, NC and WC of OSAS group were statistically higher than the control group (p < 0.001). According to logistic regression analysis; BMI, WC and NC enlargement were observed as significant risk factors for OSAS development. Risk coefficients were determined 5.53 for NC, 4.48 for WC and 2.22 for BMI. Cut-off point values for anthropometric obesity indices as OSAS determinant were recorded as below: BMI for male ≥ 27.7 kg/m² and female ≥ 28.9 kg/m², NC index for male ≥ 40cm and female ≥ 36 cm, WC index for male ≥ 105cm and female ≥ 100cm. Conclusion: BMI, NC and WC enlargement were determined as significant risk factors for OSAS development. This was an initial study to determine the cut-off points of which increase the OSAS risk in BMI, WC and NC index in Turkish adult population.

P3916

Validation of a new auto adjusting bilevel algorithm in complicated sleep disordered breathing patterns

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Introduction: OSAs patients are increasingly affected by high pressure demands, coexisting central events and periods of hypoventilation. Fixed bilevel treatment could fail due to changing pressure demands or non-compliance. To facilitate treatment with a variable level device with auto-trilevel principle and fixed backup rate was developed. We validated therapeutic efficacy and subjective comfort. Methods: In a multicentre, open, controlled trial 26 patients with complicated sleep disorders were analyzed. After diagnostic PSG patients were treated with an automatic bilevel device (SOMNOvent auto-S®/Weinmann Germany) which automatically adapts pressure levels within defined PDiff- (IPAP-EPAP) limits and EEAP-limits. Results: 26 patients (7.1 ± 4.3 ± 4.2 ± 7.0 (p < 0.001). Obstructive and central apneas dropped significantly (33.0 ± 28.4 vs 1.5 ± 2.2 vs 0.1 ± 0.4, p < 0.001, respectively). ODI sank from 33.4 ± 25.1 to 10.2 ± 12.0 (p < 0.001). Respiratory arousals lowered from 15.0 ± 15.0 to 7.3 ± 1.5 (p < 0.001). The majority of patients rated the bilevel device as good (45 or 4) or very good (6) in a different clinical centres and considered the auto adjusted device mostly equal or superior to the conventional therapy. Conclusion: The novel bilevel algorithm proved to treat sleep related breathing disturbances in our patients comfortably and at least as effective as manual bilevel settings. Continuous automatic adjustment to the changing pressure demands might provide a therapeutic benefit. Further investigations are recommended to find out which type of patients benefit most.

P3917

Alternative method for non-invasive automatic positive airway pressure therapy in OSAS patients

Lisette Rohling1, Michiel Eijsvogel2.

Introduction: APAP has generally been accepted as an alternative to CPAP in the treatment of OSAS. Meta-analysis has shown that APAP can control OSAS as effectively as CPAP. It remains to be examined whether greater reductions of the mean pressure can be attained by using the lowest possible minimum level and by limiting the maximum pressure to a different extent [1]. Objective: The aim of this study is to investigate whether a new adjusted mode of APAP lowers the mean applied pressure so compliance will increase. Methods: New diagnosed OSAS patients are selected for a single blind randomized cross-over trial. Patients receive for 12 weeks two different APAP therapies, CPAP and restricted APAP (RAPAP). Prior to starting up PAP therapy patients receive a manual CPAP PSG titration. The titration night is used to set the CPAP and RAPAP. The RAPAP pressure is set 2 cmH2O around the titrated pressure [2]. After 6 weeks there is a transition to the other PAP therapy. Data is collected by questionnaires like ESS, Quebec Sleep Questionnaire (QSQ) and SF-36, REMstar Auto (Respironics) data, and home polygraphy. Results: 39 OSAS patients were recruited of which already 21 completed the study. After 6 weeks with RAPAP by mean OSQ, ESS and AHl was improved significantly. Similar effects were achieved with CPAP. Compliance showed similarities between therapies (RAPAP: 6.6 [4.3-7.9] h/night, p = 0.13). The mean applied pressure during RAPAP was 8.5 [6.0-11.5] cmH2O and for CPAP 8.5 [5.5-12.4] cmH2O (p = 0.17).

Conclusion: Analysis of 21 patients showed that RAPAP and CPAP therapy has similar treatment effects in OSAS patients. RAPAP fits the current therapy. References: [1]: Randerather W. Respiration 2000;67:272. [2]: Netzer NC. Sleep Breath 2010.

P3918

Detection of bed-exit events using a new wireless bed monitoring assistance


Objectives: To assess the capability of using Heasys, an innovative wireless bed monitoring assistance that records body movements, presence and temperature, in the detection of bed-exit events and body position changes at night. Design: Descriptive study. Settings: Sleep laboratory for patient’s recording and home for healthy volunteers. Participants: Twelve patients referred for suspicion or treatment of sleep disordered breathing and 5 healthy subjects.

Measurements: Complete polysomnography was recorded during one night in patients and during two nights in healthy volunteers. Heasys sheet was placed under the fitted bed sheet in a non-constrictive way. During the second night, healthy subjects were asked to get out of bed at least 2 times for a minimal duration of 3 minutes. Results: Heasys allowed the detection of all bed-exit events in patients and volunteers (sensitivity: 100%, and specificity: 85%). When bed-exit events were defined by the lack of the presence signal combined with absence of motion and a dip in temperature, sensitivity and specificity of Heasys were 92 and 100% in patients and volunteers. Heasys detected body position changes recorded by polysomnography respectively in 84 and 98% of the cases. Additional recorded motions were mainly related to leg movements or arousals.

Conclusion: In this small feasibility study, we can conclude that Heasys is an effective innovative device allowing bed-exit events detection in adult patients and healthy volunteers.

P3919

Reliability of apnea/hypopnea index (AHI) determined by two different auto-CPAP in patients with obstructive sleep apnea syndrome (OSAS)

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Current Auto-CPAP devices retain information on their use, pressure, leaks and respiratory events and can operate also as CPAP. We evaluated reliability of AHI values recorded by two devices (Auto-Set Spirit II - 22 pts and REMstar auto M by ResMed) and compared them with those recorded by the Emblettia, in a group of 37 consecutive adults with OSAS (mean age: 58 yrs; 14 F; BMI range: 24-61). Each patient underwent the following procedures: a. baseline ambulatory recording by Emblettia; b. 3-7 nights recordings by Auto-CPAP; c. 3-7 nights recordings by CPAP; d. ambulatory recording by Emblettia while using CPAP titrated on the basis of the Auto-CPAP records. Respiratory events were assessed by manual analysis of Emblettia traces or based on at least 4 nights records of Auto-CPAP devices. We selected only nights during which patients used the device at least 5 hrs and leaks were < 0.5 L/s. Baseline AHI ranged between 9 and 91 ev/hr. The 95th percentile airway pressure as determined by the Auto-CPAP device was 9.5 ± 1.5 cmH2O. The AHI measured by CPAP during 4 nights was 3.9 ± 1.7 (AI: 1.1 ± 1.2; HI: 2.8 ± 1.8) The AHI during CPAP was 2.2 ± 1.1 (AI: 0.7 ± 1.6; HI: 1.5 ± 1.7). Difference plots for Bland and Altman analysis were 1.7 for AHI, 0.4 for AI and 1.3 for HI. Mean difference between AHI values measured during CPAP and measured by Auto-Set Spirit II and REMstar auto M was significantly different (2.32 ± 0.76; p < 0.015). The results of this study suggest that AHI values measured by CPAP in OSAS are reliable as compared to those measured by a portable recorder and that small but significant differences exist between different CPAP devices.

P3920

Effects of reduced lung volumes and age on oxyhemoglobin nocturnal desaturation in obstructive sleep apnea patients before and after CPAP treatment

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Aim: To analyze determinants of nocturnal desaturation in obstructive sleep apnea (OSAS) patients before and after CPAP treatment.

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Introduction: Continuous positive airway pressure (CPAP) is an effective treatment for symptomatic moderate-severe obstructive sleep apnea (OSA). More recently, automatic positive airway pressure (APAP) devices are being used instead of CPAP on the premise that automatic device pressure would improve compliance although this has not been proven.

Aims: Evaluate 3-month compliance in OSA patients treated with APAP

Methods: Symptomatic patients with OSA [Apnea hypopnoea index (AHl) >10 and Ewthrop Sleep Score (ESS) >10] were offered APAP therapy and monitored
prospectively for 3 months. Their APAP data was downloaded at 2 weeks and 3 months. Data was analysed using Spearman’s test and multiple regression.

**Results:** APAP therapy was initiated in 26 patients (22 men) with a mean (SD) age of 51 (11.7) years. Mean AHI was 44.5 (25.5) and mean ESS was 12 (4.7). Mean compliance at 3 months and 2 weeks was 307 (130) and 330 (96) minutes respectively. Median (range) number of consultations over 3 months was 2 (1-9). Compliance at 2 weeks was significantly correlated to compliance at 3 months (p<0.001). Compliance at 3 months was also significantly correlated (p<0.002) to the number of consultations with sleep physiologists during this period (telephone and in person).

Other factors such as age, sex BMI, initial AHI and mean APAP did not influence compliance on multiple regression.

**Conclusions:** Short and medium term compliance is very good in our cohort. Compliance at 2 weeks predicts 3 month compliance which is in keeping with other studies.

Compliance was also found to be related to intensity of technical support suggesting that careful follow up will improve compliance.

**P3926**
Comparison of CPAP treatment and oral appliance therapy in patients with severe OSA
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**Aim:** The aim of this study was to investigate the effects of anthropometric measurements and orthonolaryngological examinations on the appropriateness of and the choice between OAT (oral appliance therapy) and CPAP treatment in patients diagnosed with severe OSA (obstructive sleep apnea syndrome).

**Material and methods:** The patients diagnosed with severe OSA (n=23) were enrolled in the present study and divided into two groups as OAT (n=11) and CPAP (n=12) by the random envelope method. Then, the patients who were ineligible for OAT were assigned to CPAP treatment, thus constituting a third group (n=7). They were examined by CPAP at one month and underwent controls at 3 and 6 months.

At the first month control, the patients who showed no improvement of AHI or those who could not tolerate the treatment were shifted to the other treatment.

**Results:** There were no significant differences between the treatment groups in terms of demographic characteristics, orthonolaryngological examinations and nasopharynx CT. It was found that, of PSG findings, REM was increased and AHI and stage 2 sleep were decreased during the first month of treatment in all treatment groups (p>0.05). All treatment groups showed improvement in oxygen saturation, which reached statistical significance only in the CPAP group (p<0.05).

**Conclusion:** We concluded that anthropometric changes and results of orthonolaryngological examinations had no effect on treatment choice in patients with severe OSA. Since CPAP treatment is more effective in patients with severe OSA, OAT would be more appropriate in patients who can not tolerate CPAP treatment.

**P3927**
Validation of the efficacy of an oral appliance for the treatment of obstructive sleep apnea in Brazil
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**Introduction:** Various studies in sleep disorders and the physiopathology of OSA has demonstrated the important role that dentistry could play in improving the lifespan of individuals with OSA.

**Objective:** To validate, in Brazil, the use of an oral appliance (OA) to treat OSA and primary snoring.

**Methods:** A retrospective study was carried out on 69 patients presented all OSA degrees or primary snoring, who were fitted to PMPsitioner between 2000 and 2010. The diagnosis and degree of severity were established by a polysomnogram (PSG) prior treatment and the efficacy of OA therapy verified by another PSG after a minimum of 6 month of OA usage. Sleepiness was evaluated by Epworth Sleepiness Scale (ESS) questionnaire prior to treatment and at the follow up.

**Results:** Patients were divided in two groups, snoring group (SG) with 7 patients and OSA group with 62 patients. Snoring patients showed no statistical results for ESS. Patients in OSA group, AHI <5 was found in 25 (40%) patients, AHI <10 was found in 52 (84%) patients, and AHI <15 was found in 60 (32.3%) patients. Among mild patients, the mean AHI reduced from 12±2.0 to 3±3.2±0.6 <p<0.001, among moderate (33%) patients, the mean AHI reduced from 21±6.3 to 4.6±3.8 and among severe (12%) patients, the mean AHI reduced to 44±13.5 to 10.0 to 4.3. The mean minimum oxygen saturation (SaO2 nadir) for the entire OSA group, increased from 81±1.8 to 86±1.7 <p<0.001. The ESS values reduced significantly from 13.5±5.6 to 8.4±3.5 (<p<0.05).

**Conclusion:** We can support the efficacy of adjustable oral appliance in the OSA therapy in Brazilian patients. Various physiologic variables have improved.
the therapeutic impact of VO is not studied. The results of the present study indicate that the effect of VO on the degree of UA collapse as assessed during DESE tends to be adverse, causing collapse in the majority of patients.

P3930

The effects of breathing manoeuvres on the trigeminocardiac reflex reversal of artificially induced supraventricular tachyarrhythmias into the sinus rhythm

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Trigeminocardiac reflexes (TCR) elicited from the intranasal, facial orbital, perinasal or forehead regions are known by a spectrum of respiratory and circulatory vegetative effects which are dominated by strong vagal reflex bradycardia that can be effectively used in the reversal of certain supraventricular tachyarrhythmias (SVTs). The present aim was to examine the effects of inspiratory (IA) and expiratory apneas (EA) (20-25 s breath holding on TLC or FRC levels, respectively) and Valsalva manoeuvre (VM, 20s occl. pressure 35 mmHg) on the mechanism of reversal from SVTs by facial cold TCR (cold gel, 10°C for 60 s). AVNRT (15 s) and AVN (2 s) were used at 15 cm s-1, 1, MSa/d) were induced by atrial electrical impulses (2-4mA, 1ms duration, 600 ms period) and/or by isoprenalin (1-5µg/min, i.v.) in 17 patients (18-62 y) while recording ECG, heart rate (HR) and blood pressure (BP). Data showed that TCR+EA and TCR+IA increased both bradycardic (26%, vs. 6-4%, as well as pressor effect (13-4% vs. 10-4%) of TCR. Moreover, TCR+IA and TCR+VM increased both the speed and success rate of SVTs reversal (by 11-15%, 45-2%, vs. 33%). When applied alone IA, EA or VM decreased HR in SVTs (11.2±3.1%, n=19, 8.6±2.1%, n=9, 16.2±3.1, n=19, M±SD) and raised BP (6-19%). Occasionally, EA (18%) and IA (21%) reversed SVTs into the normal rhythm similar to TCR (27-45%) and VM (26%). The role of intrathoracic pressure changes and other reflex mechanisms underlying SVTs reversal by inspiratory and expiratory manoeuvres and TCR are discussed.

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Moreover, TCR+IA and TCR+VM increased both the speed and success rate of SVTs reversal (by 11-15%, 45-2%, vs. 33%). When applied alone IA, EA or VM decreased HR in SVTs (11.2±3.1%, n=19, 8.6±2.1%, n=9, 16.2±3.1, n=19, M±SD) and raised BP (6-19%). Occasionally, EA (18%) and IA (21%) reversed SVTs into the normal rhythm similar to TCR (27-45%) and VM (26%). The role of intrathoracic pressure changes and other reflex mechanisms underlying SVTs reversal by inspiratory and expiratory manoeuvres and TCR are discussed.

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Is obstructive sleep apnea syndrome a risk factor for pulmonary thromboembolism?

P3931

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There is no study demonstrating the relationship between OSAS and venous thromboembolism (VTE). The aim is to evaluate OSAS in patients with pulmonary embolism (PE) and OSAS as a risk factor for PE. In the department of chest diseases of Duzce University Hospital, 50 patients with PE were evaluated for the frequency of OSAS, prospectively. Polysomnographic was performed to clinically stable 30 patients agreed to participate in the study. Apnea-hypopnea index (AHI) more than 5 was defined as OSAS. 30 patients (14 women, 16 men, 25-85 age) were included in study. There were 24 patients with non-massive PE (58%), 3 patients with submassive PE (%10), 2 patients chronic PE (%6.7) and 1 patient with massive PE (%3.3), respectively. %56.7 of the patients (17/30) OSAS were detected. The percent of patients with moderate and severe OSAS (AHI >15) was 52.7 (8/30). The patients with no known major risk factors for PE had significantly high rates OSAS compared to those with having major risk factors (respectively, 9/30; 12/21 and 5/19, p<0.05). The majority of group with major risk factor for VTE was found low. (66-13 and 52-15, p: 0,015) There was no significantly difference for gender, weight and body mass index between the groups, who have OSAS and without OSAS. The difference for gender, weight and body mass index between the groups, who have OSAS and without OSAS were have a great risk of developing serious PTE.

Discussion: Our results may have been influenced by some patients having other significant factors that not all patients had the blood tests done. An elevated D-dimer was not found to be significantly associated with a diagnosis of PE in our study. Troponin and CRP also had no diagnostic significance. Raised Urea, integral to the severity scoring in community acquired pneumonia, was, however, significant.

P3934

The frequency of the chronic thromboembolic pulmonary hypertension and associated risk factors

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The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) are yet to be accurately evaluated and may be significantly underestimated. The study enrolled 325 consecutive patients with acute pulmonary thromboembolism (PTE). In all patients PTE were diagnosed objectively and the mean follow-up was 16.3 months (range, 6.50.7 months). Outpatient visits and hospitalisation records of all patients were examined. Especially, data on recurrence, mortality and CTEPH were collected. Symptomatic patients were investigated for CTEPH with echocardiography, lung perfusion scintigraphy and CT angiography according to proposed algorithms in updated guidelines of pulmonary hypertension. The frequency of symptomatic CTEPH was 4.6% after the first episode of PTE. Symptomatic CTEPH were established in 37.5% of the patients who have a history of proven PTE and in 6.2% of the patients with previous isolated DVT. The percentage of patients with residual chronic thrombus was 48% at 3 months, 27.4% at 6 months, and 18.2% at 12 months after the diagnosis of PTE. There was significant relationship between recurrence and presence of residual thrombus

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142. Prediction of pulmonary thromboembolism

P3932

Late-breaking abstract: Significant association between protein C promoter region polymorphism and susceptibility to pulmonary thromboembolism in a Chinese Han population

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Pulmonary thromboembolism (PTE) is a common clinical problem that is associated with substantial morbidity and mortality. Because protein C (PC) play an essential role in regulation of thrombin activity, we investigated the role of PC polymorphism in patients with pulmonary thromboembolism. One hundred and ten cases of PTE and one hundred and ninety healthy control in Chinese Han population were genotyped for three polymorphisms (-1654C/T, -1641A/G and -1476C/T) of PC promoter. Using Binary logistic regression analysis, genetic risk factor, which was homoygous carriers of genotype TT (the SNP site -1654C/T of the PC gene, and conventional risk factors (“operation and trauma” and “operation and trauma”) were independent predictors of the development of PTE. PC gene SNPs (-1654C/T, -1641A/G and -1476C/T) in control region are probably associated with the susceptibility to PTE in Chinese Han population. The homoygous carriers of genotype TT of -1654C/T was significantly associated with the outcome of PTE, which together with “operation and trauma” and “operation and trauma” were a great risk of developing serious PTE.
after 3 months. At the time of acute event; a systolic pulmonary artery pressure (sPAP) >50 mm-Hg, presence of widespread thrombus, history of previous VTE, idiopathic PTE and high uric acid levels were associated with increased risk of development of CTEPH in univariate analysis. In multivariate analysis, sPAP > 50 mm-Hg was found that 10-fold increased for CTEPH. As a serious complication CTEPH develops in an important part of the PTE patients. Especially, closer monitoring of high risk patients is important for early diagnosis and treatment.

P3935
Prediction of pulmonary embolism in the pulmonary departments: Clinical prediction rules
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Background: Diagnosis of pulmonary embolism (PE) requires clinical probability assessment. In recent years, a great number of clinical prediction rules have been issued.

Objective: To evaluate the effectiveness of the Geneva and the Revised Geneva score in PE diagnosis in pulmonary departments.

Patients and methods: A retrospective study of 53 consecutive patients admitted for clinically suspected PE. We evaluated the clinical probability of PE for all patients for whom a CT pulmonary angiography (CTPA) was performing. Patients were divided into 2 groups: Group 1 (G1: n = 25) with no confirmed PE, the second group (G2: n = 28) with confirmed PE.

Results: In a prospective cohort of 607 patients with a first episode of proximal DVT and PE, CTPA was performed in 198. The incidence of recurrent VTE was analyzed: sex, the clinical presentation as PE or proximal DVT, the presence of hormonal change (contraception, pregnancy or hormonal substitution treatment); OR=0.9, 95%CI [0.6-1.3], p=0.65.

Conclusion: A major independent risk factor of recurrent VTE is the presence of widespread thrombus, history of previous VTE, idiopathic PTE and high uric acid levels. In multivariate analysis, sPAP > 50 mm-Hg was found that 10-fold increased for CTEPH. As a serious complication CTEPH develops in an important part of the PTE patients. Especially, closer monitoring of high risk patients is important for early diagnosis and treatment.

P3936
Age is a major risk factor of venous thromboembolism (VTE)
Nicolas Bizien, Elise Noel-Savina, Cecile Tromeer, Aurelien Delluc, Dominique Mottier, Christophe Leroyer, Francis Couturard.

Introduction: Age is a major risk factor of developing a first episode of VTE; however, the impact of age on the risk of recurrent VTE remains controversial.

Method: In a prospective cohort of 607 patients with a first episode of proximal deep vein thrombosis of pulmonary embolism, we aimed to evaluate if age of VTE was an independent risk factor of recurrent VTE. The role of other risk factors was analyzed: sex, the clinical presentation as PE or proximal DVT, the presence or the absence of provoking risk factors, factor V Leiden (FVL) and prothrombin gene mutation (PGM) was analyzed. All the episodes of first VTE and recurrent VTE were diagnosed according to predefined, validated and standardized criteria.

Results: During a mean follow-up of 36 months, 95 (15.6%) patients had recurrent VTE. In multivariate analysis, for each year that the patient was older, the risk of recurrent VTE increased by 3.0% (OR=1.03; 95%CI [1.01-1.05], p<0.001). When age of patients was divided into quartiles, the relative risks of VTE were as follows: [64-74 years]: OR=2.9, 95%CI [1.3-6.9]; [75-99 years]: OR=3.1, 95%CI [1.3-7.5]; p<0.01; quartile of reference [18-44 years]. Men and women had similar risks of recurrence, excepted women who had VTE in association with hormonal change (contraception, pregnancy or hormonal substitution treatment); OR=0.2, 95%CI [0.1-0.4]; p<0.001). FVL and PGM were not associated with an increased risk of recurrent VTE (OR=1.1; 95%CI [0.5-2.1]; p=0.9).

Conclusion: Age is a major independent risk factor of recurrent VTE.

P3937
Improving the diagnostic yield of PE using the BTS pathway: The experience of a UK district general hospital
Craig Batista, Timothy Ho. Department of Respiratory Medicine, Frimley Park Hospital NHS Foundation Trust, Camberley, Surrey, United Kingdom

In 2003, the British Thoracic Society developed an algorithm for investigating PE, based on risk stratification (low, intermediate and high), selected D-Dimer use and Computed Tomography Pulmonary Angiography (CTPA). For low and intermediate patients a negative D-Dimer is reliable in excluding PE, avoiding unnecessary irradiation. Despite this, the positive diagnostic yield within our organisation remains below 25%. To understand this low yield, we carried out a retrospective analysis of medical patients who underwent CTPA during November 2010.

Method: The medical records of all patients admitted with suspected PE who underwent CTPA were analysed. Each patient’s risk was retrospectively scored according to BTS guidance and adherence to the BTS diagnostic pathway was noted.

Results: 37 patients underwent CTPA: 15 low, 14 intermediate and 8 high probability. In 21 (95.6%) of 22 patients with no confirmed PE, the second group (G2: n = 28) with confirmed PE.

Conclusion: Our study suggests that adherence to BTS guidance may improve diagnostic rates for PE and reduce the number of inappropriate CTPAs.

P3938
Clinical presentations of pulmonary embolism in young adults
Natalia Stoeva, Diana Lekova, Vassa Hristova. Internal Department, Tokuda Hospital Sofia, Sofia, Bulgaria

Pulmonary embolism (PE) is considered an age related disease and clinical observations are directed predominantly towards older patients. Our study examines clinical presentations of PE in young (under 40 years) adults. We retrospectively analyze 133 adult patients hospitalized in Tokuda Hospital Sofia for the period Feb 2007 to Jan 2011 in whom PE was diagnosed by multidetector computer pulmonangiography. 24 (18%) of them are under 40 years. We analyze this group (young group) and compare it to the group of patients older than 40 (old group). All patients of the young group are white race, and are ethnic Bulgarians. 19 (79.2%) are men and 5 (20.8%) - women (vs.55males:50% and 54females: 49.6% in the old group). 424 patients have previous surgical intervention, and 2/4/ underlying diseases. The other 18/24 (75%) have no triggering events. 16/24 were examined for inherited and acquired thrombophilies and in 13 (81%) thrombophilies were found (3 with Plasminogen activator inhibitor mutation, 2 with Leiden mutation, 1 prothrombin gene mutation, 4 with combined heterogenous mutations, 2 with P.S deficiency and 1 with antiphospholipid antibodies). Mean Wells probability score is 5.24±1.7 (4.2±1.2±5.5 in old group; p=0.02); mean revised Geneva score is 8.41±3.91 (vs. 8.62±3.95; p=0.73); 11/24 (45%) have concomitant US confirmed DVT (vs. 4%). More than half (54%) have massive PE, understood as involvement of more than 50% of pulmonary circulation. In our study PE adults in young patients in most cases arises spontaneously, it is due to inherited and acquired thrombophilies, and affects more men than women. Using the Wells probability score, PE in young adults is more easily recognizable than in older adults.

P3939
The potential benefits of outpatient investigations of suspected pulmonary embolism (PE)
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Background: Computed Tomography Pulmonary Angiography (CTPA) is the recommended investigation for non-massive pulmonary embolism (PE) and guidelines suggest outpatient management in stable patients with PE [1]. Outpatient investigation of such patients may also be potentially possible.

Aim: To ascertain the proportion of patients admitted to our hospital with suspected PE that could potentially have been investigated as outpatients.

Methods: Retrospective analysis of all CTPAs performed over an 8-week period from December 2009 in a UK university teaching hospital.

Results: 198 CTPA scans were performed. PE was confirmed in 30 (15.2%). The mean time period of inpatient stay before obtaining their CTPA was 5.5 days (SD 6).

Table 1

<table>
<thead>
<tr>
<th>Time from admission to CTPA</th>
<th>≤48 hours</th>
<th>48–72 hours</th>
<th>&gt;72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>76 (38%)</td>
<td>52 (26%)</td>
<td>70 (35%)</td>
</tr>
<tr>
<td>Confirmed PE, n (%)</td>
<td>9 (5.5%)</td>
<td>11 (6%)</td>
<td>10 (5%)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Time from CTPA to discharge</th>
<th>≤48 hours</th>
<th>&gt;48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>51 (26%)</td>
<td>125 (63%)</td>
</tr>
<tr>
<td>Confirmed PE, n (%)</td>
<td>4 (8.5%)</td>
<td>26 (13%)</td>
</tr>
</tbody>
</table>
51 (26%) patients were in hospital for ≤48 hours post investigation, only 1 of whom had confirmed PE. 

**Conclusion:** A careful assessment to identify patients that can safely have an outpatient CTPA and decreasing time to scan for in-patients would increase efficiency.

A 20% reduction in time from admission to CTPA would result in an annual saving of £2.400.000 (approximately £410.000).

If we postulate that patients discharged ≤48 post CTPA were well enough to have been investigated as outpatients, doing so would have saved at least 288 bed days, enough to bed 8 weeks, equating to 1728 bed days (£540,000) over a year.


**P3940**

**Hyperglycemia as an independent predictor of mortality in acute pulmonary embolism**

Julia-Cristina Roca1, Viviana Aursulescu1, Mihai Roca1, Mihai-Dan Datcu2,  
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**Introduction:** Acute pulmonary embolism (APE) is a life threatening disease and one of the main causes of in-hospital mortality. Hyperglycemia secondary to diabetes mellitus, impaired glucose tolerance or stress-induced, occurs frequently in critically ill patients and is associated with adverse outcome. The relationship between hyperglycemia and outcome in APE patients has not been clearly defined.

**Aim:** The purpose of the study was to determine the association between hyperglycemia and risk - adjusted mortality in APE patients.

**Methods:** We conducted a prospective, cohort study, between 1 January 2004 and 31 December 2009. The patients with APE, admitted in the 1st Medical Cardiology Clinic, in “St Spiridon” University Hospital, Iasi were included. Hyperglycemia was defined as an admission or in-hospital fasting glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations.

**Results:** During the study period, we enrolled 326 patients with APE. Mean age of the patients was 62.3 years (range 16 - 95 years), 197 (60%) were females. 30 (9%) were in shock at admission and 36 (11.04%) had diabetes mellitus diagnosis before admission. Fifty seven patients died during hospital stay (17%). Multivariable analysis showed that hyperglycemia was an independent predictor for in-hospital mortality in APE patients (p <0.05).

**Conclusion:** Hyperglycemia is an independent predictor for in-hospital mortality in APE.

**P3941**

**Assessment of pulmonary embolism severity index, D-dimer, cardiac biomarkers and multi detector computed tomography findings in patient with pulmonary thromboembolism**

Burcu Koyden1, Fusun Alatas 1, Huseyin Yildirim1, Guntulu Ak 1,  
1Emergency Medicine, University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania; 3Pneumology, University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania

**Introduction:** Clinical manifestations and status on the pretest probability in patients with pulmonary thromboembolism

Burcu Koyden1, Fusun Alatas 1, Huseyin Yildirim1, Guntulu Ak 1,  
1Emergency Medicine, University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania; 3Pneumology, University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania

**P3942**

**Improvement of thromboprophylaxis by attaching printed thrombosis risk assessment tool and recommendations to patient’s hospital charts**

Mehmet Hossein Rahimi-Rad, SeidSoma Seidsalehi, Shabnam SeidSahle

**Introduction:** We conducted a prospective, cohort study, between 1 January 2004 and 31 December 2009. The patients with APE, admitted in the 1st Medical Cardiology Clinic, in “St Spiridon” University Hospital, Iasi were included. Hyperglycemia was defined as an admission or in-hospital fasting glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations.

**Methods:** We conducted a prospective, cohort study, between 1 January 2004 and 31 December 2009. The patients with APE, admitted in the 1st Medical Cardiology Clinic, in “St Spiridon” University Hospital, Iasi were included. Hyperglycemia was defined as an admission or in-hospital fasting glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations.

**Results:** During the study period, we enrolled 326 patients with APE. Mean age of the patients was 62.3 years (range 16 - 95 years), 197 (60%) were females. 30 (9%) were in shock at admission and 36 (11.04%) had diabetes mellitus diagnosis before admission. Fifty seven patients died during hospital stay (17%). Multivariable analysis showed that hyperglycemia was an independent predictor for in-hospital mortality in APE patients (p <0.05).

**Conclusion:** Hyperglycemia is an independent predictor for in-hospital mortality in APE.

**P3943**

**Clinical manifestations and prediction rules in patients with pulmonary embolism and prior respiratory disease**

Renata Baez-Saldana, Monica Velazquez-Uncal, Isela Cisneros-Chavez, Octavio Abanto-Valencia. Hospitalizarn, Instituto Nacional de Enfermedades Respiratorias, Mexico, Distrito Federal, Mexico

**Introduction:** Presently, little is known about de effect of prior respiratory disease on clinical manifestations and status on the pretest probability in patients with pulmonary embolism.

**Objective:** To describe clinical manifestations and status on the clinical prediction rules in patients with pulmonary embolism and prior respiratory disease.

**Methods:** We retrospectively analysed 118 cases with diagnosis of PE, in a referral hospital of respiratory diseases in Mexico City from 2007 to 2009. Clinical information was taken form medical records and Wells and Geneva prediction rules were used to categorize the patient’s clinical pretest probability of PE.

**Table 1**

<table>
<thead>
<tr>
<th>Wells probability criteria</th>
<th>Total population n = 118</th>
<th>With prior respiratory disease (16/47%)</th>
<th>No prior respiratory disease (42/53%)</th>
<th>P value p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>26 (22%)</td>
<td>16/29</td>
<td>10/17</td>
<td>0.005</td>
</tr>
<tr>
<td>Intermediate</td>
<td>51 (43%)</td>
<td>25/45</td>
<td>26/48</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>33 (28%)</td>
<td>17/23</td>
<td>16/30</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>36 (31%)</td>
<td>21/37</td>
<td>15/35</td>
<td>0.048</td>
</tr>
<tr>
<td>Extremely likely</td>
<td>23 (19%)</td>
<td>14/30</td>
<td>9/34</td>
<td></td>
</tr>
<tr>
<td>Geneva probability criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>32 (27%)</td>
<td>10/18</td>
<td>12/17</td>
<td>0.384</td>
</tr>
<tr>
<td>Intermediate</td>
<td>72 (61%)</td>
<td>43/77</td>
<td>29/44</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>91 (78%)</td>
<td>51/72</td>
<td>40/21</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** A simple intervention can improve VTEP rate in setting that electronic alert is not available. VTEP is underused despite improvement still there is high gap between evidence and practice.

**Acknowledgements:** We would like to thank JA. Caprini (j-caprini2@aol.com) for giving permission to use Risk Assessment Tool.
P3944

D-dimer testing and pre-test probability scoring in the diagnosis of venous thromboembolism

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Introduction: With easy availability of bedside markers of venous thromboembolism (VTE) like D-dimer, widespread use of these tests often without pre-test probability scoring (PTPS) has become common practice in the diagnostic pathway of VTE.

Aims: We set out to assess how effective D-dimer testing is in predicting the likelihood of VTE and whether PTPS adds any further value to D-dimer testing.

Method: Consecutive patients with suspected VTE were included for a 3 week period - 90 records were analysed where a D-dimer test (Roche Test kit) was performed as part of the diagnostic pathway in the admissions unit of a teaching hospital providing acute medical services to a population of 450000.

Results: 40 D-dimer tests were positive, 50 negative; 14 with positive tests had radiological confirmation of VTE (CT Pulmonary Angiogram, Ventilation-Perfusion scan or Doppler Ultrasound Scan of the legs), 8 with negative tests still went to have radiological imaging because of high clinical suspicion but all were negative. Thus sensitivity was 100%, specificity 65.79%. Only 31 patients had PTPS, 18 had high or intermediate PTPS with positive D-dimer but only 8 had VTE (44.4%); 1 with low PTPS and positive D-dimer had VTE; 5 with high or intermediate PTPS but negative D-dimer had no VTE. The remaining had low PTPS with no VTE.

Conclusions: D-dimer is a very sensitive and reasonably specific tool to aid VTE diagnosis in appropriate clinical presentations but further aids need to be developed to rule out the possibility of VTE with a negative D-dimer but does not seem to add any further value in patients with a positive D-dimer, hence PTPS should be included in the interest of patient safety.

Discussion: There was no overall difference in all cause mortality at 2 years post CTPA for suspected PE between those who had a PE and those who did not. Mortality was equally high (15%) in both groups, regardless of presence or absence of PE at the time of investigation.

None of the biochemical markers we studied were associated with increased mortality. Only 220 (48%) and 174 (38%) patients had D-dimer and Troponin (known to be associated with increased all-cause mortality) measured respectively, although 369 (80%) had CRP measured. This may explain why an elevated Troponin was not associated with increased mortality in our study.

P3947

Trends in the incidence and case fatality of pulmonary embolism in hospitalized patients during 1997-2008 in China: A multicenter registration study

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Background: In China, the National Cooperation Project of Prevention and Treatment for Venous Thromboembolism provided valuable information about the epidemiology of PE. So, comprehensive assessment on the incidence and case fatality of PE in hospitalized patients can be made firstly.

Methods: Between January 1997 and December 2008, consecutive patients, admitted to the inpatient ward with a diagnosis of suspected PE, were registered from 60 hospitals. The data was collected prospectively including demographic data, types and results of diagnosis methods and prognosis. All of patients were identified with a discharge diagnosis of PE based on the St. Anthony’s ICD-9 diagnostic codes.

Results: From January 1997 to December 2008, hospitalization data were collect for 1,8306 patients diagnosed with PE while there were 16,972,182 discharged patients. The annual incidence increased sharply from 0.03% in 1997 to 0.13% in 2003, then persisted 0.14%. Conversely, the case fatality was decreasing apparently from 25.11% in 1997 to 8.65% in 2008.

Conclusion: The actual incidence of PE among the hospitalization patients in China was 0.14%. Evidence suggests that a substantial decline in PE-specific mortality and the annual age-adjusted mortality from PE has been shown as a result of the prevention and treatment of PE.
<table>
<thead>
<tr>
<th>Presentation</th>
<th>PE</th>
<th>No PE</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained dyspnoea</td>
<td>48</td>
<td>182</td>
<td>230</td>
</tr>
<tr>
<td>Shock</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pleurisy/haemoptysis</td>
<td>9</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Disproportionate dyspnoea</td>
<td>28</td>
<td>131</td>
<td>159</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
<td>145</td>
<td>175</td>
</tr>
<tr>
<td>Blush</td>
<td>3</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>521</td>
<td>643</td>
</tr>
</tbody>
</table>

2-way contingency table of reason for test (rows) by CTPA result (columns)

For risk factors, only a history of VTE influenced likelihood of PE (Odds ratio 7.46, CI 2.99-18.3, p<0.001).

Unexplained dyspnoea 48 182 230
Shock 4 4 8
Pleurisy/haemoptysis 9 42 51
Disproportionate dyspnoea 28 131 159
Other 30 145 175
Blush 3 17 20
Total 122 521 643

Chi-squared (df 5) 5.385, p=0.272, not significant.

Diagnostic accuracy of unenhanced and gadolinium-enhanced magnetic resonance imaging for acute pulmonary embolism diagnosis: Results of the "BEM-EPS" study

Sensitivity of unenhanced MRA was 96.7% (95% CI, 90.8% to 99.6%) for reader 1 and 95.1% (95% CI, 90.2% to 98.1%) for reader 2. Specificity was 63.6% (95% CI, 50.0% to 76.0%) for reader 1 and 77.1% (95% CI, 62.6% to 89.3%) for reader 2. Positive and negative predictive values were 72.0% (95% CI, 60.3% to 81.3%) for reader 1 and 54.9% (95% CI, 43.3% to 65.5%) for reader 2. The area under the receiver operating characteristic curve was 0.86 (95% CI, 0.81 to 0.90) for reader 1 and 0.84 (95% CI, 0.79 to 0.89) for reader 2.

Conclusions: Sensitivity of unenhanced MRA for the diagnosis of PE was 96.7% (95% CI, 90.8% to 99.6%) for reader 1 and 95.1% (95% CI, 90.2% to 98.1%) for reader 2. Specificity was 63.6% (95% CI, 50.0% to 76.0%) for reader 1 and 77.1% (95% CI, 62.6% to 89.3%) for reader 2. Positive and negative predictive values were 72.0% (95% CI, 60.3% to 81.3%) for reader 1 and 54.9% (95% CI, 43.3% to 65.5%) for reader 2. The area under the receiver operating characteristic curve was 0.86 (95% CI, 0.81 to 0.90) for reader 1 and 0.84 (95% CI, 0.79 to 0.89) for reader 2.

Results: Sensitivity was better for proximal VTE than distal PE (96.1%) and good agreement (Kappa: 0.62), whereas perfusion sequences showed lower sensitivity, specificity and agreement.

Magnetic resonance imaging (MRI) has not been yet fully evaluated for diagnosis of pulmonary embolism (PE).

Aims: To evaluate MRI performance for PE diagnosis by reference to 64-detector CT angiography (CTA) in patients with clinical suspicion of PE.

Intervention: MRI including, unenhanced ECG-gated, perfusion and angiographic sequences was performed within 24 hours from CTA and were interpreted by two independent readers blinded to CTA results.

Measures: Sensitivity, specificity evaluated globally and for each sequence. Inter reader agreement evaluated with the kappa statistics.

Results: Among 300 patients included, 274, with a conclusive CTA, completed the whole MRI protocol, of which 103 had PE on CTA (prevalence: 37.6%). 76 of the 274 MRI examinations (28%) were judged inconclusive by reader 1 and 83 (30%) by reader 2. Sensitivity and specificity of conclusive MRI on global readings were 84.5% (95% CI, 79.4% to 90.1%) and 99.9% (95% CI, 95.1% to 100.0%) for reader 1 and 78.7% (95% CI, 68.2% to 87.1%) and 100% (95% CI, 96.7% to 100.0%) for reader 2, respectively. Sensitivity was better for proximal (97.7% to 100%) than for segmental (69% to 15%) and sub-segmental PE (21% to 33%). Angiographic sequences showed the highest performance and agreement (Kappa: 0.77). Unenhanced sequences, although less sensitive, showed high specificity (96.1%) and good agreement (Kappa: 0.62), whereas perfusion sequences showed lower sensitivity, specificity and agreement.

Conclusion: MRI demonstrates high specificity, even for unenhanced sequence and acceptable sensitivity for PE diagnosis at the cost of a 28% to 30% rate of inconclusive result.
residual asthmatic inflammation in the peripheral airway. The ECP levels in late-phase sputum (255±2.97 lg/1 at study entry) significantly decrease 60.8±4.7 lg/l (p<0.038) and 50.7±4.84 lg/l (p=0.049) at 4 and 8 weeks after switching to treatment with the BFC, respectively. The FeNO levels (76±6.49 ppb at study entry) also significantly decreased 29.1±15.7 (p=0.017) at 8 weeks. The R5-R20 and AX values of ICS parameters also significantly improved after 8 weeks.

Conclusions: This study suggests that the BFC may give better control of residual eosinophilic inflammation in the distal airway compared to SFC therapy.

P3952 Montelukast as add-on therapy may improve some indices of small airways involvement in uncontrolled asthmatics

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Background: Several studies suggest an involvement of small airways in asthma that may contribute to poor disease control.

Aim: To assess whether montelukast improves indices of small airways involvement and clinical outcomes in asthmatics under regular therapy with medium-high doses of inhaled corticosteroids and long-acting β2-agonist.

Subjects and methods: 240 non-smoker asthmatics underwent, at baseline and after one-month open label therapy with montelukast, FEVI, Single Breath Nitrogen Washout for phase III slope (DN2); multiple flows exhaled nitric oxide (NO); eosinophils in sputum (EO%;), alveolar-arterial differences of respiratory gases (AaDO2, AaDCO2); asthma control obtained by symptoms (S) and variability of peak expiration flow (APEF) monitoring.

Results: Patients were divided in controlled (n=7 well controlled, n=10 partially controlled) and non-controlled (n=7), according to GINA guidelines. After one month therapy with montelukast, in a) controlled group, therapy significantly reduced APEF (18.2±6.9 vs 13.1±4.8 l/s (p<0.007); b) in non-controlled group, therapy significantly reduced only AaDO2 (32.1±7.9 vs 25.8±7.7 mmHg, p=0.034). Patients were also divided in two other groups according to the number of abnormal values of small airways involvement (DN2, CαNO and AaDO2) at baseline: 0-1 vs 2-3 abnormalities. Montelukast reduced APEF (21.8±7.8 vs 17.4±11.2 l/s, p<0.001) only in patients with 2-3 abnormalities in small airways indices.

Conclusions: Montelukast might improve both functional and clinical indices of small airways involvement, in controlled and non-controlled asthmatics and this might be associated with some effects on small airways.

P3953 The eXpeRience registry: Monitoring the “real-world” effectiveness of omalizumab in allergic asthma

Gert-Jan Braam1, D. Leuven1, Chien-Wen Chen1, Robert Maykut4, Panayiotis Georgiou2, Guy Peachey2, 1Cardio-Thoracic and Vascular Department, University of Pisa, Pisa, Italy; 2Institute of Clinical Physiology, CNR, Pisa, Italy; 3CNR, Pisa, Italy; 4Medical Department, UCB Pharma NV, Brussels, Belgium

The observational, global eXpeRience registry was established to collect “real-world” data from omalizumab-treated allergic asthma patients. The registry aims to collect data on effectiveness/safety of omalizumab for up to 2 years during standard clinical practice.

This interim analysis included 876 patients (mean age, 44.9 years) with uncontrolled allergic asthma. The final analysis is expected to be presented at the American Thoracic Society's (ATS) 2011 Conference.

Results: The included patients were 54% female and 46% male. The mean time on omalizumab treatment was 23.4±20.9 months. As of 31 March 2011, 47.3% of patients were on the recommended dose of 150 mg, 35.1% were on a dose of 300 mg, and 17.6% were on a lower dose of 150 mg every other week. A total of 77.3% of patients had at least one severe asthma exacerbation during the study period. The 54 included trials comprised 13,460 patients (2,795 children) with allergic asthma. The mean duration of allergic asthma was 19.5 (SD 13.7) years; mean total IgE serum levels: 316.6 (SD 419.13) IU/mL.

Conclusions: Omalizumab is an effective add-on therapy for patients with allergic asthma, with a manageable safety profile. Omalizumab improves asthma control and quality of life, even in patients with frequent exacerbations. Omalizumab is associated with a reduction in the risk of severe asthma exacerbations, and a reduction in the risk of hospitalization for asthma exacerbations. Further studies are needed to investigate the long-term safety of omalizumab.

P3954 Omalizumab and malignancy: Interim results from the EXCELS study

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Background: Omalizumab is a biologic for the treatment of moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids. At the time of FDA approval, the incidence of malignant neoplasms was higher among patients who had received omalizumab (0.5%) compared to placebo (0.2%) in clinical trials.

Objective: The EXCELS study is an FDA postmarketing commitment to evaluate the long-term safety of omalizumab.

Methods: EXCELS is an ongoing prospective observational study of approximately 5000 omalizumab-treated and 2500 non-omalizumab-treated moderate-to-severe persistent allergic asthma patients aged ≥12 years from 448 US centers who are followed up for up to 5 years. All reported potential malignancies are reviewed by an independent oncology panel. The primary analysis includes confirmed, incident-study-emerging primary malignancies.

Results: This analysis of malignancy rates was based on interim study report 6 (data through 11/30/2010) which comprises 18,860 person-years in the omalizumab cohort and 10,947 person-years in the non-omalizumab cohort. Both cohorts had an average follow-up of 3.8 person-years. The incidence of study-emerging primary malignancy was 12.78 and 14.48 per 1000 person-years in the omalizumab and the non-omalizumab cohorts, respectively, corresponding to a rate difference of -1.70 per 1000 person-years (95% CI -6.63 to 2.21).

Conclusions: In this analysis, the incidence of malignancy was similar in the omalizumab and non-omalizumab cohorts. These interim results are preliminary and the study is still ongoing. Because the study is observational, selection and other biases cannot be excluded.

Funding Source: Genentech, Inc and Novartis Pharmaceuticals Corp.

P3955 Factors influencing the relative effect of leucotriene receptor antagonists (LTRA) and inhaled corticosteroids (ICS) as monotherapy in persistent asthma: A systematic review

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Objectives: To compare the safety and efficacy of LTRA with ICS in patients with asthma across age groups, over time, baseline severity and ICS dose.

Methods: In a systematic review until 2010, a randomised controlled trials comparing LTRA to ICS for ≥30 days in children and adults with asthma. The primary outcome was exacerbation requiring systemic steroids. Secondary outcomes included lung function, asthma control, adverse effects and withdrawals.

Results: The 54 included trials comprised 13,460 patients (2,795 children) with mild (42%) or moderate (58%) airway obstruction. In 84% of trials, LTRA was compared to a low ICS dose over 4-52 weeks. Compared to ICS, 48% more patients treated with LTRA suffered exacerbations requiring systemic steroids (RR 1.48; 95% CI 1.18, 1.85). There was no significant difference in the magnitude of effect between children and adults, ICS dose, and age. The benefit of ICS over LTRA was greater in patients with moderate vs. mild airway obstruction (RR=2.03 vs. 1.25, p<0.01). FEVI, symptoms, night awakenings, rescue β2-agonist use, symptom-free days, and quality of life favour ICS at almost any point of time. The use of LTRA was associated with more than a 2-fold increased risk of withdrawals due to poor asthma control (RR 2.58; 95% CI 2.01, 3.30). Both options were equivalent in the risk of overall side effects.

Conclusions: ICS remains superior to LTRA to prevent exacerbations and improve asthma control, irrespective of age group, ICS dose, and duration of treatment. However, the benefit of ICS is significantly greater in patients with moderate airway obstruction.

P3956 Real-life effectiveness of beclomethasone dipropionate/formoterol extra-fine combination in adult patients with persistent asthma

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Background: Efficacy and safety of extra-fine beclomethasone dipropionate 100 μg/formoterol 6 μg pMDI (BDP/F) in adult patients with moderate-to-severe persistent asthma has been demonstrated in double-blind randomized controlled clinical trials.

Objective: To assess real-life effectiveness of BDP/F on asthma control.

Methods: Non-interventional, prospective, open-label, multicentre study in Bel-
gium from December 2008 till December 2010. Patients were enrolled by pneumo-
logists and general practitioners (GPs). Visit 1 (Day 0): demographic and
baseline asthma control data collection, initiation of BDP/F treatment; Visit 2
(Day 21-240) and Visit 3 (Day 214-420) evaluation of asthma control by patients
(Juniper ACQ7) and investigators (GINA asthma control score), assessment of
BDPF safety/tolerability.

Results: 619 patients were enrolled: mean age 48±16.9 years, 54% female, 22.8%
smokers, mean FEV1 % pred 78.6±20.0%. At Visit 3 the mean daily beclomeha-
sone dose was 266±127 µg.

Table 1. Evolution of ACQ7 and GINA asthma control scores

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACQ7 (mean± SD)</td>
<td>2.24±1.13</td>
<td>1.05±0.82*</td>
<td>1.00±0.83*</td>
</tr>
<tr>
<td>GINA score improved (% patients)**</td>
<td>46.8</td>
<td>40.3</td>
<td></td>
</tr>
<tr>
<td>GINA score stable</td>
<td>3.66</td>
<td>41.7</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001 vs Visit 1; **vs Visit 1.

Similar improvements in asthma control, evaluated as patient-reported ACQ7
score, physician-rated GINA asthma control score, were observed in patients
recruited by pneumologists and by GPs. Treatment-related non-serious adverse
drug reactions were reported in 16 patients (2.6%).

Conclusion: The results of this study demonstrate the real-life effectiveness of
effective BDP/F in adult patients with moderate-to-severe persistent asthma.

**P3957**

Effect of budesonide/formoterol, budesonide and terbutaline on exercise-induced bronchoconstriction in mild intermittent asthma

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Background: Omalizumab (OMA) treatment has been shown to be effective in
patients with severe allergic asthma (SAA), but published data beyond the first
year of treatment are scarce.

Objectives: To examine the persistence rate (PR), to identify reasons for discon-
tinuation and to determine the response rate (RR) and the clinical effectiveness
beyond the first year of OMA treatment.

Methods: Of 105 patients, who were on OMA treatment at the end of the 52w ob-
servational PERSIST study (Respir Med 2009; 103: 1633), 53 (51%) participated in
this study. A retrospective medical chart analysis was performed at approx. 16, 52,
and 68w after the end of the PERSIST study (up to 12w of treatment). Measure-
ments included PR, patient-reported Global Evaluation of Treatment Effectiveness
(GETE), Asthma-related Quality of Life Questionnaire (AQLQ), and systemic
glucocorticosteroid (gCSc) use, emergency room (ER) visits and hospitalizations
for severe exacerbations.

Results: The PR at 12w was 84.9%. Treatment was discontinued in 3 cases by
patient decision (1 relocation, 1 AE, 1 non-compliance with office visits), in 3
patients by joint patient/physician decision (2 complete asthma control, 1 AE)
and in 2 patients due to non-OMA related death. Where data were available, RR
(good/excellent GETE) was >85%. Absolute change of ≥0.5 point in AQLQ score
remained >90% from 6w up to 12w, less than 18.9% of patients required gCSc, there
were no ER visits and only 1 hospitalization during the evaluation period.

Conclusions: These preliminary results indicate a high PR with OMA beyond the
first year of treatment under “real-life” conditions in SAA patients in Belgium.

**P3960**

Plasma and urinary concentrations of inhaled salmeterol in healthy and
persons with asthma – Quantifying a doping limit

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Copenhagen, Denmark; 2Department of Pharmaceutical Chemistry, Aker
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Hospital, Copenhagen, Denmark

Background: Salmeterol is a long acting β2agonist that is used in treatment of asthma. β2agonists are on WADA and IOC’s prohibited list, but salmeterol is allowed in therapeutic doses by inhalation. The prohibited list however contains no urinary limit for salmeterol, which gives athletes the opportunity to inhale unlimited doses of salmeterol. Large doses of β2agonists may have ergogenic effects and therefore a quantification of a urine salmeterol limit is necessary.

**Purpose:** To find plasma and urinary concentrations of inhaled salmeterol in inhalation therapeutic dose 100 µg in healthy and persons with asthma. To discuss a urinary concentration limit for inhaled salmeterol on the prohibited list.

**Methods:** 10 persons with asthma (A) and 10 healthy subjects (C) were enrolled, age 24±6.3.9. The subjects underwent two visits. First visit was a pre-examination with a metacholine provocation and lung function test. On second visit the sub-
jects inhaled 100 µg salmeterol (Seretide®) as a single dose. Blood samples were acquired at baseline and 0.5, 1, 2, 3, 4 and 6 hours after administration. Urinary samples were collected at baseline and 4, 8, 12 and 24 hours after adminis-
tration. Plasma and urine samples were analyzed by liquid chromatography mass spectrometry.
Results: The peak median urinary concentration was found after 4hrs reaching 0.38±0.26 mg/mL in A and 0.38±0.22 mg/mL in C. Peak median plasma concentration was 0.07±0.03 mg/mL for A and 0.06±0.03 mg/mL in C. No differences were found between the groups.

Conclusions: Urine salmeterol peak 4h after administration by inhalation. We propose a salmeterol urine limit of 0.82 mg/mL in in doping controls.

P3964 The effect of liposome inhalation on non-invasive oxidative stress markers in patients with bronchial asthma
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Background: The liposome inhalation demonstrates an antioxidant activity in the treatment of various diseases, confirmed both by experimental and clinical studies. The aim is to carry out a prospective study of antioxidant features of liposome inhalation in patients with the exacerbation of bronchial asthma.

Materials and methods: We enrolled 50 patients (age=37.7±7.5 year, men=64%) with bronchial asthma (FEV1>70%, steroid-naive) in prospective comparison study. All patients were divided in two groups: group 1 contains 25 patients, who received a liposome inhalation by compression nebulizer once a day (300 mg of phospholipids in each administration); group 2 contains 25 patients, who received a traditional therapy (control). Antioxidant activity was determined by the estimation of the exhaled nitric oxide level (ENO) and total nitrite/nitrate (TNN) in exhaled breath condensate before and after the investigation period.

Conclusions: There was a significant decrease of ENO level in group 1 from 31.8±2.4 to 7±1.1±4 ppb (p<0.001) after the observing period. In group 2 the ENO level was decreased from 29.7±3.9 ppb to 25.0±2.5 ppb (not significant). Patients in both groups had significantly lower levels of TNN before the study (7.7±0.9 μM) and 8.4±1.1 μM respectively). After liposome administration the TNN level in group 1 decreased to 9±0.6 μM (p<0.01) as well as in control group it was at the same border (7.7±1.4 μM).

Conclusion: The results obtained demonstrate that liposome inhalation administered once a day during 14-days period has a significant antioxidant effect in patients with mild-to-moderate bronchial asthma.

P3965 Quantitative IgE levels in asthma and implications for treatment with omalizumab. Are the cutoffs to narrow?
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The use of omalizumab is constrained by the narrow quantitative parameters in its use. This study looks at experience in a small pulmonary-practice as regards comparison study. All patients were divided in two groups: group 1 contains 25 patients, who received a liposome inhalation by compression nebulizer once a day (300 mg of phospholipids in each administration); group 2 contains 25 patients, who received a traditional therapy (control). Antioxidant activity was determined by the estimation of the exhaled nitric oxide level (ENO) and total nitrite/nitrate (TNN) in exhaled breath condensate before and after the investigation period.

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Conclusion: The results obtained demonstrate that liposome inhalation administered once a day during 14-days period has a significant antioxidant effect in patients with mild-to-moderate bronchial asthma.

P3966 Stability and achievement of asthma control with higher doses of inhaled corticosteroids regular treatment
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Background: Uncontrolled asthma is characterized by variability. Previous GOAL study demonstrated that once asthma is achieved, the future risk of instability is greatly reduced. Higher stability (lower variability) in asthma control is also associated with a lower future possibility of unscheduled healthcare resource use. In the study, we attempted to increase inhaled combined agent doses initially and hypothesized that stability was positively associated with the level of control achieved.

Methods: This was a prospective study and new diagnosed asthma patients were included and randomized into two groups. One group was treated with higher doses (HD) one month then shifted to guideline-practice (GP) treatment and another was treated with GP therapy model. Peak expiratory flow (PEF) asthma, symptom control (ACT) and exacerbation times were measured. The follow-up time was 1/2 year.

Results: 39 patients were treated with HD and 40 patients were GP therapy policy. PEF change were significantly improved in HD group compared with GP (56±17 vs. 45±19, p=0.04). The obvious improvement especially in initial 2 months (77±39 vs. 52±23, p=0.01). There were significantly differences in ACT change and exacerbation frequency in patients with mild and moderate persistent asthma using HD therapy.

Conclusion: Our findings demonstrated that patients with HD treatment were more improved and stabilized than patients with previous conventional therapy policy. Further evaluation should be performed on patients and long term follow-up to confirm the higher doses’ efficiency.

P3967 Comparison of the efficacy of ciclesonide with budesonide in mild to moderate asthma patients after step-down therapy
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Inhaled corticosteroids are the most widely used controller treatment for asthma, and is the stepping down level when asthma is controlled with combination therapy. Ciclesonide is an inhaled corticosteroid with on-site lung activation that provides anti-inflammatory activity. The aim of this study was to compare the efficacy of ciclesonide (CIC) with budesonide (BUD) in 142 adult patients with mild to moderate asthma who were well-controlled with a combination of inhaled corticosteroids and long-acting β2-agonist. They were randomized to receive once-daily ciclesonide 320mg (n=73) or twice-daily inhalations of budesonide 200 mg (n=69) for 12 weeks. The forced expiratory volume in one second (FEV1), maximum mid-expiratory flow (MMEF) and asthma control test (ACT) score were evaluated. Tolerability and ranked stratification of patient and physician were assessed. At the end of study, the withdrawal rate of CIC group (26.4%) was significantly less than that of BUD group (42.7%, p=0.02). There was no difference of FEV1 and MMEF throughout 12-week treatment period in CIC group. In BUD group, FEV1 decreased significantly at 4-week (1.8±0.1 L, n=59, p<0.0006) and 12-week of treatment (1.9±0.1 L, n=39, p<0.01) compared with baseline (2.0±0.1 L, n=69). MMEF decreased significantly at 4-, 8- and 12-week compared to baseline in BUD group. ACT score decreased significantly at 4-week of treatment in BUD group compared with baseline. There was no difference of ACT score over the 12-week period in CIC group. In conclusion, ciclesonide was more effective and better drug adherence than budesonide in the stepping-down treatment of asthma from combination therapy.
The effect of GSK2190915, a 5-lipoxygenase activating protein inhibitor, on the early asthmatic response to inhaled allergen

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Background: GSK2190915 is a potent 5-lipoxygenase activating protein inhibitor, thereby interfering the synthesis of leukotrienes and 5-oxo-ETE.

Objective: To assess the effects of GSK2190915 on the allergen induced early asthmatic response (EAR).

Methods: 19 patients with mild asthma were enrolled in this 3-centre, double-blind, 3-way crossover study. They took 10 and 50 mg GSK2190915 and placebo orally, once daily for 3 days, in randomised order. On Day 3 they had an inhaled allergen challenge.

Results: GSK2190915 had a significant effect on the EAR, the treatment difference from placebo for 10 mg was 0.212 L (0.044, 0.379) and for 50 mg was 0.409 L (0.242, 0.576) for minimum FEV1, in the 2 hours after allergen inhalation. The magnitude of the effect with 50 mg GSK2190915 in this study was comparable to that observed with 100 mg on the EAR in a separate study [1]. Safety and tolerability were good.

Conclusion: GSK2190915 has shown a significant, dose related, inhibition of the EAR to inhaled allergen.

References:

Clinical Trials.gov identifier NCT00812773

P3967 Asthma control and lung function after step down from high dose ICS/LABA combination therapy

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Rationale: Guidelines recommend asthma treatment to be adjusted to the lowest dose maintaining control.

Objectives: To evaluate whether lung function and asthma control can be maintained in patients treated with high dose ICS/LABA combination after step-down.

Methods: Prospective, multinational, randomized, open label, parallel group controlled trial. Patients treated with high dose (1000/100 μg daily) fluticasone/salmeterol (FP/S) either DPI or pMDI entered a 2-month run-in with FP/S Diskus 1000/100 μg daily. Controlled patients (GINA) were treated either with FP/S Diskus 500/100 μg daily or extraline beclometasone/formoterol (BDP/Fp) pMDI 400/24 μg daily for 6 months. Morning PEF was the primary outcome.

Results: 378 patients were evaluated for ITT; previous treatment was DPI in 87% of patients. Equivalence was shown in morning PEF at the end of treatment (difference between means 2.49 L/min; 95% CI -1.33 to 18.42). Morning PEF remained above 95% predicted throughout the study, though absolute values decreased (414.4 to 397.1 L/min for BDP/Fp; 429.7 to 394.6 L/min for FP/S; p=0.001). Asthma control was maintained in the majority of patients with no worsening in FEV1 measured at clinics, symptoms score, use of rescue medication and no differences in any parameter including exacerbations.

Conclusions: Patients controlled with high dose ICS/LABA DPI can be stepped-down to medium dose either DPI or extraline pMDI maintaining asthma control.

P3968 Risks of diabetes mellitus and hyperglycaemic adverse events in patients with asthma taking inhaled corticosteroids

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Background: A recent study of patients with lung disease and with prescriptions for inhaled corticosteroids (ICS) detected a 34% increased risk of diabetes mellitus. Methods: A retrospective analysis evaluated the double-blind, placebo-controlled, clinical trials in asthma (duration > 3 years) in patients >24 years of age, involving budesonide (BUD) or BUD/formoterol (26 trials, n=9607 for BUD; n=9296 for placebo). A supplementary dataset evaluated all double-blind, non-placebo controlled trials in asthma (duration >3 months), involving the use of ICS (60 trials, n=33496 for BUD, n=2773 for fluticasone propionate [FP]). Cox proportional hazards regression modelling, both adjusted and not adjusted by study, was used to estimate the relative risk of ICS on diabetes mellitus/hyperglycaemia adverse events (AEs) or serious adverse events (SAEs) in both the primary and supplementary datasets.

Results: In the primary dataset, the occurrence of diabetes mellitus/hyperglycaemia AEs was 0.13% for BUD and 0.13% for placebo (HR 0.98 [95% CI 0.38–2.50] p=0.96); the occurrence of diabetes mellitus/hyperglycaemia SAEs was 0% for BUD and 0.05% for placebo. In the supplementary dataset, the occurrence of diabetes/hyperglycaemia as AE and SAE was 0.19% and 0.03%, respectively. There was no increased risk with higher doses of BUD, nor any difference between BUD and FP. The risk for diabetes mellitus/hyperglycaemia increased with age, BMI and disease severity.

Conclusion: This retrospective analysis of all double-blind trials with BUD in asthmatic patients did not demonstrate any increased risk of diabetes mellitus/hyperglycaemia with BUD treatment. Funded by AstraZeneica.

P3969 Increased incidence of pulmonary embolism in severe asthma

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Introduction: Many patients with severe asthma need inhaled (ICS) and chronic oral (OCS) corticosteroids for asthma control. OCS are associated with hypercoagulability and increased risk of venous thromboembolism (VTE). Also asthma itself is associated with a prothrombotic state (Brims 2009).

Hypothesis: The incidence of VTE is increased in asthma, and associated with asthma severity and OCS use.

Methods: 166 Outpatients with mild-moderate asthma (mean (range) age 49yr (18-80), 56% female, all using ICS), and 139 patients with severe asthma (52yr (18-77), 62% female, 39% using OCS) from 3 clinics in the Netherlands and Davos, Switzerland, were consecutively included in a cross-sectional study. Patients completed a questionnaire about previous VTE, risk factors and medication use. All VTE events were objectively diagnosed. Data were compared with the available incidence (ages 50-54 yr) in the general population (Naess 2007).

Results: Deep vein thrombosis (DVT) occurred in 3 and 2 patients with severe and mild-moderate asthma resp. and pulmonary embolism (PE) in 11 and 3. Overall incidence was 1.77/1000 person yr in severe asthma vs 0.7 in mild-moderate asthma and 1.03 in the general population. The relative risk of PE for severe asthma was 5.5 (95% CI: 1.24-24) and independently associated with >2 exacerbations/yr (RR 12.63, 1.48-107) and chronic OCS use (RR 8.21, 1.57-43). The risk of DVT was 0.50 (0.13-1.96). In mild-moderate asthma risks were not increased.

Conclusions: Patients with severe asthma have a 5.5-fold increased incidence of pulmonary embolism, which is associated with exacerbation frequency and chronic oral corticosteroid use.

Implication: Pulmonary embolism may be important in the prognosis and management of severe asthma.
414. Drug delivery and pharmacokinetics II

P3970
Effects of hydrocortisone on acute beta-blocker and histamine induced bronchoconstriction
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Introduction and objectives: The benefits of chronic beta-blockade in asthma have recently been questioned, however concerns of bronchoconstriction persist with the greatest risk after first dose. We investigated the safety of acute exposure to propranolol in asthmatics, sequentially challenged with histamine to mimic an asthma exacerbation and evaluated the role of hydrocortisone in potentiating salbutamol reversibility.

Methods: Persistent atopic asthmatics, ≤1000g/day beudesonide performed a randomised double-blind placebo-controlled crossover study. Following 10mg or 20mg of oral propranolol, patients received 400mg iv. hydrocortisone or placebo, followed by histamine challenge with nebulised salbutamol 5mg and ipratropium 500mcg recovery.

Results: 13 patients completed per protocol. Hydrocortisone did not potentiate salbutamol recovery post-propranolol and histamine challenge. Beta-blocker induced bronchoconstriction was demonstrated by sputum and IOS. For the placebo visit, FEV1% fell 4.7% 2hrs post-propranolol whilst R5% increased 31.3%. On both visits FEV1% and R5% returned to baseline after salbutamol post-histamine.

Conclusion: Nebulised salbutamol produced a full recovery after propranolol and histamine induced bronchoconstriction, independent of hydrocortisone use. Our findings offer reassurance to those undertaking further evaluation of chronic beta-blockade as a potential treatment for asthma.

P3971
Safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of GSK573719 inhalation powder in healthy subjects
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Ann Allen 1, Joanne Bal 2, Anne Chestroub 2, Melanie Hamilton 4, Rodger Kemptsof 2, Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Research Triangle Park, United States; 4Inhaled Product Development, GlaxoSmithKline R&D, Wuren, Hertfordshire, United Kingdom; 5Clinical Pharmacology Science & Study Operations, GlaxoSmithKline R&D, Stockley Park, Middlesex, United Kingdom; 6Discovery Biometrics, GlaxoSmithKline R&D, Uxbridge, Middlesex, United Kingdom; 7Respiratory and Immuno-Inflammation Medicine Development Center, GlaxoSmithKline Research Triangle Park, United States

Introduction: GSK573719 is a new long-acting mucinasic antagonist offering sustained 24-hour bronchodilation in development for the treatment of COPD.

Methods: In this single-centre, double-blind, parallel-group study, 36 healthy adults were randomised 3:1 to GSK573719 (250μg, Cohort 1; 750μg, Cohort 2; 1000μg, Cohort 3) or placebo as DPI once daily for 14 days.

Results: Most adverse events (AEs) were mild and all resolved during the study; the most frequent drug-related AEs were headache and pharyngolaryngeal pain (0–2 subjects per group). No clinically relevant abnormalities or changes were seen in laboratory results or vital signs. There were no clinically significant ECG abnormalities or heart rate changes. Although 41–67% of plasma PK samples were non-quantifiable, available data showed a median tmax of 5–15min, mean t1/2 (Day 14) of 26–28h (25–35h from urine PK). Although visual assessment of Ctau data suggested that steady state was achieved following 6 to 8 days of dosing, there was large data variability. Urinary excretion of unchanged GSK573719 was 1–1.5% of the total dose on Day 1 and 3.4–4.5% at steady state. Accumulation (Day 14-Day 1) was 1.5–3x on placebo PK (1.3–5x on urine PK). There was no correlation between GSK573719 systemic exposure and pharmacodynamic variables.

Conclusion: GSK573719 was well tolerated by all subjects and no safety concerns were identified even at the highest dose, supporting the continued development for COPD.

Funded by GSK (AC4106889; NCT00475436)

P3972
Safety, tolerability and pharmacokinetics (PK) of repeated doses of GSK573719 inhalation powder, a new long-acting mucinasic antagonist, in healthy adults
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Introduction: GSK573719 is a new long-acting mucinasic antagonist offering sustained 24-hour bronchodilation in development for the treatment of COPD.

Methods: To investigate the safety, tolerability and PK of repeated once-daily dosing (14 days) of GSK573719 dry powder inhalation (DPi). 13 patients completed per protocol. Hydrocortisone did not potentiate salbutamol recovery post-propranolol and histamine challenge. Beta-blocker induced bronchoconstriction was demonstrated by sputum and IOS. For the placebo visit, FEV1% fell 4.7% 2hrs post-propranolol whilst R5% increased 31.3%. On both visits FEV1% and R5% returned to baseline after salbutamol post-histamine.

Conclusion: Nebulised salbutamol produced a full recovery after propranolol and histamine induced bronchoconstriction, independent of hydrocortisone use. Our findings offer reassurance to those undertaking further evaluation of chronic beta-blockade as a potential treatment for asthma.

Funded by GSK (AC4106889; NCT00475436)
Ann Allen1, Joanne Bai2, Anne Cheshire3, Melanie Hamilton4, Rodger Kempford5.

**Objectives**: To evaluate and compare FF PK in Caucasian (Ca), Chinese (Ch) and Japanese (Jp) subjects following FF administration via a novel dry powder inhaler and i.v. infusion.

**Methods**: Open-label, randomized, two-way crossover study. Healthy male and female Ca, Ch, Jp and K subjects [N=20/group], randomized to receive OD inhaled FF (200mcg (7 days) then 800mcg (7 days)) and single i.v. 250mcg dose. PK data were obtained on D1 and/or D7.

**Results**: The average PK parameters of i.v. FF were similar in Ca, Ch, Jp and K subjects, consistent with CYP3A4 activity in each population. Inhaled FF systemic exposure was higher at both doses (AUC ratio: 1.27 to 1.75) in Ca, Ch, Jp and K subjects, compared with Ca subjects, reflecting higher bioavailability (800mcg D7: 14.3% to 16.3% and 10.4%, respectively). Deconvolution analysis suggested that inhaled FF resided in the lungs of Ca, Ch and Jp subjects for longer than in Ca subjects, a likely reason for seeing greater bioavailability. All treatments were safe and well tolerated and no marked quantitative or qualitative differences in safety endpoints between the ethnic groups.

**Conclusion**: Following inhaled FF there was higher (1.2-fold) systemic exposure in Chinese, Japanese and Korean subjects compared with Caucasian subjects, although there were no safety or tolerability consequences. Funded by GSK (HZIA13477; NCT0100597)

**P3977**

Glycoprotein MDI demonstrates comparable efficacy and safety to tiotropium DPI in Chinese, Japanese, and Korean subjects

Chadwick Orevalil, Earl St. Rose1, Shannon Stronm2, Tracy Fischer2, Michael Golden2, Mervyn Thomas3, Colin Reisner1.

**Objectives**: To determine the absolute bioavailability of FF and VI when administered in combination as FF/VI from a novel dry powder inhaler in healthy subjects.

**Methods**: In this open-label, non-randomised, three-way crossover, single-dose study, male and female subjects [N=16] received (in order) a single inhaled dose of FF/VI 800/100mcg (4 inhaletions of 200/25mcg, a single 250mcg intravenous (i.v.) dose of FF and a single 55mcg i.v. dose of VI. FF and VI pharmacokinetic data were obtained up to 48h post-dose.

**Results**: The average absolute bioavailability of FF when inhaled as FF/VI relative to i.v. FF was 15% (90% CI 13, 18). The average absolute bioavailability of VI when inhaled as FF/VI relative to i.v. VI was 27% (90% CI 22, 35). Both FF and VI were rapidly cleared and widely distributed following i.v. dosing. FF showed longer retention in the lung than VI following inhaled administration with the time for 90% of the total to be absorbed from the lung on average 35.2h and 3.8h, respectively. All treatments were safe and well tolerated even though this study evaluated multiples of the likely inhaled therapeutic dose (200/25mcg).

**Conclusion**: In healthy adult subjects the absolute bioavailability of FF was 15% and for VI was 27% following a single inhaled dose of FF/VI delivered via a novel dry powder inhaler. Funded by GSK (HZIA102934, NCT0129558).

**P3978**

No pharmacodynamic (PD) and pharmacokinetic (PK) interaction of riociguat (BAY 63-2521) and aspirin

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**Objectives**: Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is a new candidate for treatment of pulmonary hypertension (PH). Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent stimulation of sGC; and increasing sensitivity of sGC to low levels of NO. Riociguat and aspirin are likely to be used together in PH. This randomized, open-label, crossover study investigated potential PD and PK interactions between the 2 drugs.

**Methods**: Participants took 2.5 mg/day riociguat, two morning doses of 500 mg aspirin, or both treatments concomitantly.

**Results**: Eighteen healthy men (mean age 34.8 years) were enrolled. Six of 17 participants in the safety evaluation reported ≥1 treatment-emergent adverse event (AE). All AEs were mild except 1 case of moderate headache following riociguat administration. Fifteen participants were valid for PD/PK analysis. Riociguat PK was independent of aspirin coadministration. One hour after coadministration of riociguat and aspirin, the mean increase in fraction unbound was 19% for riociguat and 24% for its metabolite M1 (BAY 60-4552) indicating mild displacement by salicylic acid, the main aspirin metabolite. Effects of aspirin on bleeding time, platelet aggregation and plasma thromboxane B2 were not affected by concomitant riociguat. Riociguat alone had no effect on PD variables.

**Conclusion**: Riociguat demonstrated no clinically relevant PD or PK interaction with aspirin. Coadministration of riociguat and aspirin does not require dose adjustment. Phase 3 randomized controlled trials are investigating riociguat in chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension.

**P3979**

How can we improve patient use of inhaler devices in COPD?

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**Introduction**: “Ease of use” is traditionally seen as a key factor in COPD inhaler choice. Our aim was to assess patient and healthcare professional (HCP) needs and problems with inhalers and to offer these patients to satisfy these needs, enabling better patient adherence with maintenance inhalers.

**Methods**: 1008 HCPs and 490 patients (≥18 years) participated in an online survey. Sawtooth Software’s ACA and CBC products were used to collect, randomize and measure relative impact of features in utility values (positive vs. negative choice impacts).

**Results**: Overall, with current devices, patients indicate a lack of full certainty that they have taken the full dose correctly (rating of only 4.3 for Asthma, 5.3 for COPD; 1–7 scale). HCPs place far more importance on increasing patient satisfaction and demand than other attributes, reasoning this aids adherence. Similarly, patients want ease of use and features to aid adherence (a dose reminder and improvements over dose counters) to address their primary unmet need of uncertainty in inhaling
all doses fully. Device type (MDI, DPI, multidose, single-dose) has little impact in HCP choice (COPD HCP utilities: patient satisfaction and demand +92, multidose DPI 3, dose spacer 1). Conclusion: Issues such as dose counters and multidose vs. single-dose have little impact on physician demand. Satisfying patient need for true dose confirmation can drive patient satisfaction and adherence. Patients need devices that assure them that they have taken the full dose to be more adherent, and HCPs need devices that drive patient demand and adherence.

P3979
Patient assessments of ease of use of Genumovar® versus Aerolizer® and Handihaler®
Rainard Fuhr1, Helgo Magnusson2, David Singh3, Gonzalo de Miquel4, Cynthia Caracata5, Esther Garcia Gil6, 1 Early Phase Clinical Unit, PAREXEL International GmbH, Berlin, Germany; 2 Pulmonary Research Institute, Hospital Grosshadern, Grosshadern, Germany; 3 Medicines Evaluation Unit, University of Manchester, Manchester, United Kingdom; 4 R&D Centre, Almirall, Barcelona, Spain; 5 Clinical Development, Forest Research Institute, NJ, United States

Introduction: The Genumovar® inhaler, a multidose, dry powder inhaler, has been developed to provide reliable and effective delivery of inhaled medications including acidinium bromide, which is in clinical development for the treatment of chronic obstructive pulmonary disease (COPD).

Aim: To report data from two Phase II studies that included patient assessments of the convenience of Genumovar® versus Aerolizer® and Handihaler® respectively.

Methods: Both studies were randomised, double-blind, double-dummy, cross-over trials in patients with moderate to severe COPD. In the first study, 79 patients received treatment over seven-day periods via Genumovar® and Aerolizer®. In the second study, 58 patients received treatment over 15-day periods via Genumovar® and Handihaler®. At the end of the studies, patients were asked to evaluate their impressions of inhaler convenience.

Results: Patient assessments of the different inhalers are presented in Table 1.

<table>
<thead>
<tr>
<th>Inhaler (%)</th>
<th>Presence</th>
<th>Very easy</th>
<th>Easy</th>
<th>Definitively easy</th>
<th>Use to prepare</th>
<th>Preferred inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genumovar®</td>
<td>65</td>
<td>73</td>
<td>60</td>
<td>59</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Aerolizer®</td>
<td>54</td>
<td>19</td>
<td>45</td>
<td>43</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>Handihaler®</td>
<td>80</td>
<td>83</td>
<td>36</td>
<td>35</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Conclusions: Patient assessments of convenience were higher for the Genumovar® inhaler versus the Aerolizer® or Handihaler®.

These studies were supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

*Genumovar® is a registered trademark of Almirall S.A.

P3980
Comparison of the bronchoprotective effects of two salbutamol sulphate HFA pMDI formulations using methacholine challenge testing
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Background: Clinically, methacholine challenge has been widely used for the detection and quantification of bronchial responsiveness. This study assessed the bronchoprotective effects of two salbutamol sulphate HFA pMDI formulations using methacholine challenge.

Aim: The aim of this study was to evaluate equivalence between Salbutamol sulphate HFA pMDI (Cipla Ltd, India) against methacholine induced bronchoconstriction.

Methods: This was a randomised, double-blind, double-dummy, four period, crossover study. At each treatment visit patients administered either one puff (100 μg) or two puffs (200 μg) of either the test or the reference product. On each of the treatment days, two methacholine challenge tests were performed, one before and one 10 minutes after dosing.

Conclusions: The bronchoprotective effect of salbutamol sulphate HFA pMDI (Cipla Ltd, India) against methacholine induced bronchoconstriction was equivalent to salbutamol sulphate HFA pMDI (Ventolin Evohaler, Allen & Hanbury, UK). Both the products were safe and well tolerated.

P3981
Preference of the inhaler device and assessment of the technique among the asthmatic and COPD patients
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Different inhaler devices (IDs) are available for delivering treatments to patients with asthma & COPD. They have different technique which can easily confuse patients, resulting in incorrect use. The aim of this study was to evaluate the preference of the IDs and assessment of inhaler technique among the asthmatic and COPD patients. 300 patients (117 male:183 female) included in this study. Their mean (SD) age was 44.6 ± 16.9 years. Manly three different inhaler devices were used. Metered dose inhaler (MDI) Handihaler® (HCP) and TUR & MDI (ACE) were used. 205 patient preferred the ACE while 82 & 13 preferred the TUR & MDI respectively. The assessment of inhaler technique according to the manufacturer instruction dose shows that 156 patients were having a good technique when using MDI, while 278 and 210 patients were having a good technique when using TUR & ACE respectively. Table 1 highlights that some patients were inhaling with either very low or very high rates.

Table 1. The range of patients inhalation flow rates through the MDI, ACE and the TUR using In-Check Dial

<table>
<thead>
<tr>
<th>Flow rate (L/min)</th>
<th>MDI</th>
<th>ACE</th>
<th>TUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–60</td>
<td>13</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>60–90</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Thus they need to be trained but this may not be possible, because studies have shown that patient soon revert back to the previous technique. Even after counselling some patients may not have sufficient inspiratory effort to achieve the most desirable inhalation rate for the DPI they have been prescribed. From the results obtained we can conclude that the ACE is the most desired ID by the patients followed by the TUR & MDI. All patients were using MDI, nearly all of them having a high flow rate through it.

P3982
Pharmacokinetic evaluation of two HFA pMDI formulations of salmeterol xinafoate administered through a spacer (ACE) and multidose (MDI) Inhaler in healthy subjects
Saumya Chandran1, Nazma Morde1, Juliet Rebello1, Siddarth Chachad2, Shinivara Purandare3, Geena Malhotra1, Ratnakar Jadhav4, Krishnan Iyer2, Raghav Nuad1, 1 Clinical Research Department, Cipla Ltd, Mumbai, Maharashtra, India; 2 Contract Research Organisation, Sitec Labs Pvt Ltd, Mumbai, Maharashtra, India

Background: No pharmacokinetic studies of salmeterol HFA pMDI with a spacer device have been published. In this study comparative bioavailability of two salmeterol HFA pMDI formulations administered through a spacer device was evaluated using pharmacokinetic endpoints.

Aim: To compare the rate and extent of absorption of the test product Salmeterol xinafoate HFA pMDI (Cipla Ltd.) with that of the reference product Serevent Evohaler (supplied by Allen & Hanbury, UK), both administered using a spacer.

Methods: This was a balanced, open label, randomised, two period, single dose, crossover comparative bioavailability study in 24 healthy subjects. Eligible subjects were randomly assigned to receive a single dose of 100μg of both test and reference product administered with a spacer in a crossover manner on two treatment days. The two treatment days were separated with a washout period of 1 week. The blood samples were collected up to 24 hrs. Safety assessments including ECG, tremor assessment, serum potassium and blood glucose were also done at predefined time points. The primary endpoints were Cmax and AUC0-∞.

Results: The plasma concentration-time profile of the test product (T) was similar in shape to that of the reference product (R). The T/R ratio of the geometric mean for Cmax and AUC0-∞ was 94.54% (90% CI 87.11-102.61) and 90.68% (90% CI 83.87-98.03) respectively. The CI limits for Cmax and AUC0-∞ was well within the bioequivalence range of 80 – 125%.

Conclusion: The bioavailability of the two HFA formulations of salmeterol when administered with a spacer was comparable and both the treatments were safe and well tolerated.

P3983
The aerodynamic particle size of mometasone furoate 100 μg and 200 μg dry powder formulations
Robert Berger, Steven Li, Herbert Staudinger, Merck Research Laboratories, Merck Sharp & Dohme Corp., Kenilworth, NJ, United States

Background: Regional lung deposition of inhaled particles depends on aerody-
The impact of maximal combined inhibition. As indacaterol has demonstrated good overall safety at daily doses of up to 600 μg over a year, the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses up to 300 μg.
for once-daily treatment of COPD. IND is highly protein bound and metabolized by CYP450 and UGT1A1. Therefore, hepatic impairment or low UGT1A1 activity (Gilbert Syndrome genotype) could potentially alter clearance of IND through changes in metabolism and/or altered protein binding. Two open label studies were conducted to investigate these potential effects.

Methods: The first study was a single centre, parallel group, single dose (IND 600µg) study in hepatically impaired and matched healthy subjects. The second was a parallel 14 day repeat dose study (IND 200µg once-daily) in healthy subjects with different UGT1A1 genotypes – the fully functional [TA6,TA6] (6/6) genotype served as the control group, with the [TA7,TA7] (7/7) genotype (Gilbert syndrome) IND was determined in serum and urine (only first study) using a sensitive LC/MS/MS method. IND pharmacokinetics were compared to the respective control group, i.e. patients with mild and moderate impairment to matched healthy subjects, and UGT1A1 (7/7) to (6/6) genotype, with ratios of >1 indicating higher values in the test group.

Results: For hepatically impaired subjects the ratios (impaired vs. controls) for AUC, Cmax and and (amount excreted in urine) ranged from 0.77–1.01; no change in Δ-vivo protein binding was noted. In the comparison of UGT1A1 (7/7) to (6/6) genotype, the ratios for AUC and Cmax on Day 1 and Day 14 ranged from 0.90–1.18.

Conclusions: Taken together the pharmacokinetics of indacrinon are not significantly affected by mild and moderate hepatic impairment or UGT1A1 genotype.

P3989
In vitro comparison of aerosol characteristics of HFA albuterol (salbutamol) pressurized metered dose inhaler (pMDI) formulation from three valued holding chambers (VHCs)
Dirk von Hollen1, Lois Slator2, Kurt Nikander1, Ross Hatley 2.
Stockists: Rxplus Respplus, Ronald New Jersey, Inc., Parsippany, NJ, United States. 1Respirations Respiratory Drug Delivery (UK) Ltd, Chichester, United Kingdom

The OptiChamber Diamond (Diamond; Philips Respironics) VHC is a compact, anti-static device designed to facilitate effective pMDI aerosol delivery. This study compared aerosol characteristics from an HFA albuterol sulfate pMDI (ProAir HFA, 90 µg albuterol, Teva Specialty Pharmaceuticals LLC) alone and with an anti-static reproduction Diamond VHC, an anti-static AeroChamber Plus Z-Stat (Z-Stat; Monaghan Medical Corp.) VHC, and a conventional AeroChamber Plus (AC+; Monaghan Medical Corp.) VHC.

Six of each VHC brand were washed and air dried and six pMDIs were primed before use. For each run (n) the pMDI was actuated into the VHC or straight into the next generation impactor (NGI) (for pMDI alone - run before and after VHC before use. For each run (n) the pMDI was actuated into the VHC or straight into

The aerosol characteristics from the three VHCs were substantially equivalent and all removed significant potential throat deposition compared to use of the pMDI alone.

P3990
Fluticasone propionate/formoterol fumarate combination therapy has superior efficacy to both fluticasone and formoterol alone
David S. Pearlman1, Craig LaForce 2, Kirsten Kaiser 3, John Archer, Emma Baker. Centre of Clinical Pharmacology, St George’s University, University of London, London, United Kingdom

Introduction: Over half of COPD patients hospitalised for exacerbations have elevated blood glucose. Acute hyperglycaemia is associated with increased risk of death and prolonged hospital stay [Baker et al Thorax:61:284-9]. We investigated the effect of acute hyperglycaemia and insulin therapy on systemic inflammation. Methods: 8 stable COPD patients (4male, 66±6yrs, FEV1, 44±16%predicted) and 8 volunteers (8male, 24±5yrs, FEV1, 89±12%) with fasting glucose ≤7mM received an octreotide infusion to inhibit pancreatic function. Glucose and insulin were infused for 4 consecutive 60min periods to achieve Low glucose (fasting), low insulin (0.3mU.kg -1.min-1); high glucose (10mM above fasting levels), low insulin; high glucose, high insulin (1.5mU.kg -1.min -1); low glucose, high insulin. Cytokines were measured in blood sampled at the end of each 60min period using a Bedasystem (Bio-Rad).

Results: In COPD, high glucose, low insulin increased IP10 by 48 (12-181%) (median (interquartile range)); TNFa by 28 (8-54) from baseline (p=0.038). Additionally low glucose, high insulin suppressed IL-1α, IL-6, IL-16 and IL-1β to 4% 16% (p=0.05). Suppression of IP10 and TNFa was significantly greater in COPD patients than in volunteers (p=0.038).

Conclusion: Acute hyperglycaemia amplifies systemic inflammation in COPD, which could be detrimental during exacerbations. The anti-inflammatory potential of blood glucose control with insulin for exacerbations requires further investiga-
P3993
The relationship between acidic & non acidic gastro esophageal reflux disease (GERD) and asthma
Wald Tarsis1,2, Ishraw Alshamili1, Ebtessam Alabbesi2, Ebtessam Naas2, Mokhtar Soussai1,2,
1Respiratory Department, Tripoli Medical Center, Tripoli, Libya, Arab Jamahiriya; 2Pharmacology & Clinical Pharmacy, School of Pharmacy, Elzafar University, Tripoli, Libya Arab Jamahiriya

Asthma is a chronic airway disease characterized by airway constriction, inflammation, and hyper responsiveness to specific and non specific stimuli. GERD is a potential trigger of asthma. The relationship between asthma and GERD has been recognized for many years. Asthma symptoms; cough and chest discomfort may overlap with those of gastro esophageal reflux, making it difficult to distinguish between the two conditions. The study was designed to be for 3 months, with a monthly follow up visit to investigate the relation between asthma and acidic, non acidic GERD. Patients were divided to three groups; 1-Chang Life style (CLS) plus Omeprazole (G1) 2-Omeprazole (G2) 3-CLS (G3). GERD symptoms, Lung function (LF), asthma control test (ACT), and the asthma control questionnaires (ACQ) were measured for all patient at every visit. Fifty four asthmatic patients having the symptoms of GERD were enrolled in the study. Their mean (SD) age was 48.6 (12.6) years, 21 Patient started in G1, 21 Patient in the G2 and 12 patients in G3. From the initial results in table 1 it was clear that Omeprazole alone does not show the optimum improvement in the ACT. The results showed that the level of improvement in GERD symptoms was the same in G1&G3. In contrast 100% improvement in LF was seen in G1 while only 38% in G3, which may be due to the effect of the non acidic GERD.  

Table 1. Level of improvement of LF, ACQ, ACT and GERD symptoms in visit 2

<table>
<thead>
<tr>
<th></th>
<th>LF</th>
<th>ACQ</th>
<th>ACT</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>100%</td>
<td>78%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>G2</td>
<td>66%</td>
<td>50%</td>
<td>50%</td>
<td>23%</td>
</tr>
<tr>
<td>G3</td>
<td>38%</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

In conclusion, CLS can improve the GERD symptoms but it should be combined with the PPI in order to improve the asthma control.

P3994
Effects of pantoperazole on pulmonary function tests of chronic obstructive pulmonary disease patients, with and without gastro esophageal reflux
Farhad Malek, Raheb Ghorbani, Fatemeh Yahgobi. Internal Medicine, Semnan University of Medical Sciences, Semnan, Islamic Republic of Iran

Introduction: Association between gastro esophageal reflux (GERD) and spirometric finding in chronic obstructive pulmonary disease (COPD) is subject of controversy. The aim of this investigation is to determine the effect of proton pump inhibitor (pantoprazole) on spirometric finding of COPD patient.

Material & method: In this clinical trial, 60 COPD patients were selected and according to questionnaire divide in two groups; with and without GERD (36 and 24 patient respectively). All patient treated with oral pantoprazole 40 mg daily for eight weeks. Spirometry before and after treatment was done. FEV1/FVC, FEV1, FVC, PEF were measured in two groups.

Result: Mean PEF in COPD patients with GERD before (55.4) and after pantoprazol had significant difference (55.4, 61.5 respectively) (p = 0.009) but mean FEV1/FVC, FEV1, FVC in both groups and PEF in patients without GERD had no significant difference.

Conclusion: This study showed in COPD patient, GERD treatment with 40mg pantoprazole daily improve PEF but has no effect on other spirometric parameters.

P3995
The relationship between obesity and distal airways
Gregory Marín1, Nicolas Molinari1, Isabelle Vacher1, Philippe Godard1, Pascal Chanez2, Anne-Sophie Gamez1, Arnaud Bourdin1.
1Service des Maladies Respiratoires, CHU Arnaud de Villeneuve, Montpellier, France; 2Inserm U600, DGP, Marseille, France

Introduction: Obesity is a risk factor for asthma-like symptoms. Small airway involvement has been linked to difficulties in controlling asthma. Forced Vital Capacity (FVC) fall at PC20 has been suggested as a potent marker of distal airway abnormalities. Whether obesity is associated with increased distal airway involvement in asthma is unknown.

Hypothesis: We hypothesized that FVC fall at PC20 during a methacholine challenge was increased in overweight and obese patients with asthma-like symptoms.

Methods: 298 consecutive asthmatic adult women with asthma-like symptoms underwent a methacholine bronchial provocation test according to ATS-guidelines. 202 methacholine and FVC fall at PC20 were computed for all subjects. Bronchial Hyper Responsiveness (BHR) was considered if PC20 was ≤1600g. PC15 and FVC fall at PC15 were recorded in patients who did not achieve a 20% fall of Forced Expiratory Volume in 1 second (FEV1).

Results: A logistic regression with age, smoking and Body Mass Index showed that only obesity (BMI ≥ 30) increased the risk of BHR with an odds-ratio of 4.2 (95% CI: 1.670–12.295) (p=0.0044). BMI had no impact on the relationship between FEV1s and FVC (p=0.2960). On the other hand, BMI influenced the percentage fall in FVC at the PC15 only in patients with PC20>1600g (normal 9±13%; overweight 10±16% and obese 15±32%; p=0.0073).

Conclusion: Obesity is a risk factor for BHR in women patients with asthma symptoms. FVC fall at PC20 is not affected by the BMI. Nonetheless, in obese women with asthma symptoms but negative methacholine challenge, we observed a potential involvement of distal airways measured by the FVC.

P3996
Treatment with inhaled corticosteroids (ICS) and long acting b2-agonists (LABA) combination in patients with COPD: Possible way of optimization
Tetyana Pertseva, Kateryna Gashynova. Internal Medicine, DSMA, Dnipropetrovsk, Ukraine

Respiratory muscles dysfunction in patients with COPD could affect the inhalation technique and be one of the causes of ICS and bronchodilator’s inefficacy. Aim of study: To study the efficacy of Budesonide/Formoterol combination in dry powder inhaler (Symbicort, Astra Zeneca) in patients with COPD (stage III) with signs of respiratory muscles dysfunction. 

Study population and Methods: 20 patients with COPD III (17 men, mean age 59.9±6.3 yrs), who regularly treated by high doses of any ICS and bronchodilators no less than three month made the study sample. All patients were current smokers and had signs of respiratory muscles dysfunction (Plmax <60 kPa).

At baseline all patient withdrawn from their COPD therapy and were prescribed Budesonide/Formoterol combination 3200 mcg BID. Pulmonary function tests (FEV1, MMV, Plmax, 6MWD) and plasma C- reactive protein were evaluated before and 12 months after beginning of the study.

Results: Results are present in Table 1.

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline</th>
<th>12 months after start of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% of predicted)</td>
<td>47.5±10.4</td>
<td>52.8±11.8</td>
</tr>
<tr>
<td>MMV, (% of predicted)</td>
<td>51±7.9</td>
<td>71±6.2*</td>
</tr>
<tr>
<td>Plmax (% of predicted)</td>
<td>39.7±5.6</td>
<td>58.6±7.3*</td>
</tr>
<tr>
<td>6MWD, m.</td>
<td>273±21.6</td>
<td>359±23.4*</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>24±0.3</td>
<td>9.9±0.4*</td>
</tr>
</tbody>
</table>

*p<0.05

Conclusions: Long-term prescription of Budesonide/Formoterol combination in dry powder inhaler (Symbicort, Astra Zeneca) in COPD patients with signs of respiratory muscles dysfunction significantly increase their MMV, exercises capacity and reduce respiratory muscles fatigue and systemic inflammation.

P3997
A comparative study to evaluate the effects of salmeterol/fluticasone and formoterol/budesonide combinations on lung functions and sleep quality in asthma
Mahesh Gupta, Dhruva Chaudhary, Pooja Jindal. Pharmacology, Pt.B.D.Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India Pulmonary & Critical Care Medicine, Pt.B.D.Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

Introduction: Asthma is a prevalent chronic inflammatory disorder associated with dyspnoea, deterioration of lung functions and a negative impact on the quality of sleep. Combination treatment with a glucocorticoid and a bronchodilator is the mainstay of treatment.

Aims and objectives: To evaluate the effects of two commonly used combinations salmeterol/fluticasone and formoterol/budesonide on lung functions, dyspnoea and the quality of sleep in patients with moderately severe persistent asthma.

Methods: Sixty patients of moderate severe asthma were allocated to two different treatment groups i.e. salmeterol/fluticasone and formoterol/budesonide in a prospective, open, randomized and comparative study over a period of 6 weeks. The lung functions and Borgs dyspnoea scoring were done at the baseline and at the end of 3 and 6 weeks. Quality of sleep was assessed at the same time intervals by Pittsburgh Sleep Quality Index (PSQI) for quality of sleep and day time sleepiness by Epworth Sleep Scale (ESS).

Results: Salmeterol/fluticasone and formoterol/budesonide, caused a comparable and significant improvement in the lung functions (FEV1, FVC, FEV1/FVC and PC20). The two treatments had a highly significant and comparable improve-ment in dyspnoea. Quality of sleep as assessed by PSQI and ESS also improved significantly with both the combinations.However the salmeterol/fluticasone was relatively superior in improving quality of sleep.

Conclusions: Both the combinations were equivalent in improving lung functions & dyspnoea but salmeterol/fluticasone combination was superior with respect to sleep quality.
P3998
ACCORD COPD I: Safety and tolerability of twice daily aclidinium bromide in COPD patients
Anthony D’Urzio1, Barry Make2, Edward Kerwin3, Ludmila Rekeda4, Esther Garcia Gil5, Cynthia Caracatás6, Brian Maurer7, 8; Department of Family and Community Medicine, University of Toronto, Toronto, Canada; 12; Department of Medicine, University of Toronto, Toronto, Canada; 1; Department of Medicine, University of Toronto, Toronto, Canada; 1; Medical, Allergy & Asthma Center of Southern Oregon, PC, Portland, United States; 2; Biotestast, Forest Research Institute, Jersey City, United States; 3; R&D Centre, Almirall SA, Barcelona, Spain; 4; Clinical Development, Forest Research Institute, Jersey City, United States

Introduction: Aclidinium bromide is a long-acting muscarinic antagonist in development for COPD. Safety and tolerability of aclidinium 200 μg and 400 μg BID in moderate to severe COPD patients were assessed in this Phase III study.

Methods: In this 12-week, double-blind study, COPD patients were randomised to aclidinium 200 μg, 400 μg, or placebo BID (1:1:1). Safety was assessed via adverse events (AEs), clinical laboratory measures, vital signs, and electrocardiograms (ECGs).

Results: Baseline demographics were similar across treatment groups (N=561). The number (%) of patients with a treatment-emergent AE (TEAE) was comparable between aclidinium 400 μg, 200 μg, and placebo [85 (44.7), 93 (50.5), 97 (52.2), respectively]. COPD exacerbation was the most frequently reported TEAE in all groups (12.4%, placebo; 9.2%, 200 μg; 7.4%, 400 μg). Incidence of serious AEs was low (2.2%-4.3% for all groups). Incidence of potential anticholinergic AEs (eg, constipation and dry mouth) was low (≤3%) in both aclidinium groups and comparable to placebo. The most frequently reported AEs resulting in discontinuation were TEAEs (n=7, placebo; n=4, 200 μg; n=1, 400 μg) and dyspnea (n=2 each, placebo and 400 μg). One patient in the aclidinium 400 μg group died from metastatic lung cancer but this was not considered to be related to treatment. Changes from baseline in laboratory tests, vital signs, and ECGs, were similar across all groups.

Conclusions: Aclidinium 200 μg and 400 μg BID were safe and well tolerated throughout this 12-week study with a low incidence of systemic anticholinergic adverse events, similar to placebo. There were no differences in safety profiles between the two aclidinium doses.

P3999
Differences in adherence to inhaled steroid medication in COPD
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Objective: To study whether COPD patients on medication combining an inhaled steroid with a long-acting bronchodilator show better therapy persistence than patients with inhaled steroids alone.

Methods: This study is part of a cohort study with 3 years of follow-up (COMIC study). In total 800 patients were included. Therapy adherence was recorded from patients’ pharmacy records and was expressed as a percentage that was deemed good if it was 75-125%, sub-optimal between 50-75%, and poor below 50% or above 125%.

Results: In total 664 (83%) patients used inhaled steroids and 60.8% showed good compliance. We observed a significant difference in therapy adherence between the studied medications (p<0.001). These differences were observed between Fluticasone and Budesonide (p=0.001), Budesonide and Salmeterol/Fluticasone (p=0.001), and Salmeterol/Fluticasone and Forrtomoterol/Budesonide (p=0.002). Fluticasone had the highest percentage of patients with good adherence. For Forrtomoterol/Budesonide, Budesonide and Salmeterol/Fluticasone the percentages of good adherence were almost similar, but Forrtomoterol/Budesonide showed a higher percentage of patients with poor (＞125%) adherence, while Salmeterol/Fluticasone had a higher percentage of patients with sub-optimal adherence.

Conclusions: This study showed that a significant proportion of patients with COPD is poorly adherent to inhaled corticosteroid therapy. Furthermore, adherence rates differed significantly between the studied inhaled steroids and the combinations of inhaled steroids and LABA. Contrary to our hypothesis, the adherence did not seem to be higher in the combined medications in comparison to the inhaled steroids alone, and in some cases it was even worse.

P4000
The Dutch hypothesis, implications for treatment of chronic obstructive pulmonary disease and asthma in a biomarker, monoclonal antibody world.

Experience with IgE and omalizumab in a small pulmonary practice
Mary Lynn Ebbert, Kristin Elliott, Alicia Redford Elliott, Syed Ali, Nipurn Shah, Sridhar Reddy. St. Clair Pulmonary & Critical Care, 1210 10th Avenue, Port Huron, MI, United States

In 1961, Orie and colleagues from the University of Groningen in the Netherlands hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis and emphysema, should be considered not as separate entities but as different expressions of one disease entity. In a pulmonary practice patients with a physician diagnosis of chronic obstructive pulmonary disease (COPD) had physiologic and biochemical evaluation as part of their routine workup. They were treated with oralalumab if they were symptomatic despite adequate conventional treatment and had an elevated IgE level. Patients with COPD (n=60) who were on treatment with oralalumab for at least 6 months were asked to fill out a questionnaire from which their symptom scores (1-4) and satisfaction scores (1-5) were extracted. There was statistically significant improvement in the amelioration of both symptoms and increase in satisfaction scores (p was less than 0.01) with treatment with oralalumab. This year being the 50th anniversary of the Dutch Hypothesis, it may be appropriate to revisit this issue. Patients with COPD may benefit from evaluation and treatment with monoclonal anti-IgE antibody therapy. Randomized placebo controlled, double blinded trials are needed to help further define the role of anti IgE therapy in patients with COPD. Subsequently, the broad use of biomarkers to evaluate need for monoclonal antibody therapy may need to be reconsidered. To the treating physician and the patient the treatment outcome is more relevant than the actual diagnosis.

P4001
The effect of L-arginine on ciliary function in primary ciliary dyskinesia (PCD)
Robert Hirst, Naomi Martin, Mina Fadaee-Shohada, Claire Smith, Gwyneth Williams, Andrew Rutman, Chris O’Callaghan. Immunity, Infection and inflammation, University of Leicester, Leicester, Leicester, United Kingdom

The nitric oxide synthase substrate, L-Arginine (L-Arg), has been shown to stimulate ciliary beat frequency (CBF) in PCD [1]. However, it is unclear if this effect was universal to the common phenotypes of PCD or if it could correct the ciliary beat pattern.

Aims: To study the effect of L-Arg on the ciliary function in 3 different phenotypes of PCD.

Methods: Nasal brush biopsies were taken from 15 PCD patients (5 inner arm, 7 outer arm, and 3 transposition defects) and 3 controls. The strips of ciliated epithelium were subjected to medium 199 Control or 5nM L-Arg for 10min at 37°C. The cilia were visualised by a light microscope and recorded using a speed video. The recordings were analysed in a blinded fashion and were replayed at reduced rate for determination of CBF and cilia tip distance travelled.

Results: L-Arg treatment significantly (p<0.05) increased the CBF from (5.6±1.3 Hz) to 8.3±1.1Hz. L-Arg treatment changed the cilia (from 0.35±0.09 to 0.52±0.12 cm) in all 15 PCD patients studied. Individual phenotypes of PCD showed a variable response to L-Arg. CBF and tip distance travelled by the inner dynein arm defects were significantly (p<0.05) increased by L-Arg treatment (CBF from 6.3±1.2 to 9.6±1.1Hz; tip distance from 0.44±0.15 to 0.67±0.2cm). The CBF and tip distance of the cilia from the other defects were not statistically different.

Conclusion: L-Arg increased CBF and ciliary tip distance in PCD, an effect that was increased in those with inner dynein arm defects. The mechanism and physiological significance of the changes remain to be determined.

Reference:

P4002
Formoterol, but not indacaterol, induces transient hypoxemia in severe COPD
Roberto W. Dal Negro, Paola Pescatori, Claudia Micheleto, Silvia Tognella. Respiratory Unit, Orlando Hospital, Bussolengo, VR, Italy

β2-agonists are effective options in COPD. Mainly the short-acting compounds can rapidly induce a transient hypoxemia by affecting pulmonary vasculature. Most recent long-acting β2-agonists (LABA) were poorly investigated from this point of view.

Aim: To measure and compare the hypoxic effect of Formoterol (F) and Indacaterol (I) in moderate-to-severe COPD.

Methods: 24 ex-smoker patients (18m; mean age= 70.3±4.6; range 51-76; mean FEV1/FVC = 52.2% pred. ±9.0sd; mean FEV1=50.0±11.8sds) were studied after their written informed consent according to a double-blind, double-dummy, cross-over, randomized design. Active drugs were F120mcg and I300mcg, assayed in two different days, with a 36h-interval in between. Arterial blood was drawn in baseline; after 5’, and 30’ from F and I; FEV1 was measured at the same times.

Statistics: Friedman’s analysis of variance by ranks and Page’s test for trend, and p<0.05 accepted.

Results: See Table 1 (means ± sd).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>66.7 ±6.5</td>
<td>62.8 ±5.8</td>
<td>62.3 ±7.1</td>
</tr>
<tr>
<td>I</td>
<td>67.1 ±4.6</td>
<td>66.4 ±5.7</td>
<td>65.2 ±5.2</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>49.9 ±11.8</td>
<td>52.7 ±10.5</td>
<td>53.1 ±11.2</td>
</tr>
<tr>
<td>I</td>
<td>49.6 ±11.6</td>
<td>52.7 ±10.7</td>
<td>54.4 ±11.5</td>
</tr>
</tbody>
</table>

Discussion: Both F and I induced rapidly an equal (pneas) and significant (p<0.001) bronchodilation. The trends for PaO2 changes were significantly different with the
two drugs (p<0.04): F induced a sudden, substantial hypoxemia lasting at least for 30 s, changes following I were negligible.

Conclusions: 1) the safety of I1 is emphasized; 2) the peculiar chemical structure of I1 and the fact that it behaves as a nearly full β₂-adrenoceptor agonist likely contribute to explain its ineffectiveness in terms of β₂-agonist hypoxemia in COPD.

P4003
An audit on emergency oxygen administration and safety issues
Rajesh Kumar Yadavalli, Nadine Anwar, Brian Bradley. Thoracic Medicine, Royal Bolton Hospital, Bolton, Lancashire, United Kingdom

Background: British Thoracic Society (BTS) guidelines on Emergency Oxygen (O2) in 2008 highlighted the importance of safe prescription and administration of O2. We audited our practice focusing on the documentation, prescription and complications in a busy district general hospital.

Methods: Audit was performed on patients admitted to the medical admission unit over a period of 3 months between Jan 2010 to Mar 2010. Patients who had O2 administration order in the unit chart and received O2 were selected and monitored from admission to discharge.

Results: 56 patients in total were studied. 46% had assessment for the risk of Co2 retention before O2 started. Only 34% had documentation of target O2 saturations. Documentation of Device in 66%, Flow in 71% and Paco2 in 32% of cases. 96% of drug charts had no prescription of O2. There is no documentation how long O2 should be given in all the cases. 20 (35%) patients had inappropriate administration of O2; No need for O2-10, More O2 than needed-9 and Less O2 than needed-1. 3 patients developed Type 2 respiratory failure and needed Non-invasive ventilation. There were no mortalities.

Conclusions: We identified safety issues whilst administering Emergency O2 and need to improve in our documentation, prescription on drug charts and administration. Patients at risk of Co2 retention would have arterial blood samples after starting O2. Drug charts were modified adding oxygen in 2 areas: Regular and PRN sections and also include device, flow, FinO2, target saturations and how long to give O2. Flow charts on how to administer and adjust O2 were placed in all the wards including medical admission units.

Repeated mandatory educational training on O2 administration to all medical, nursing and allied health care professionals were started.

P4004
No difference observed in the risk of malignancy in patients exposed to omalizumab compared with controls
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Previous pooled data from the omalizumab clinical trial programme (Phase I–III clinical studies) showed a numerical imbalance in cancers arising in omalizumab recipients. The incidence of malignancies in the omalizumab group was similar to that expected in the general population but higher compared with control, raising a concern on the effect of omalizumab on the risk of malignancy. 7432 patients (4254 omalizumab, 3178 placebo) were included. Total observation times censored at first malignancy were 3382 and 2473 patient-years for omalizumab and placebo, respectively. Malignancy rates per 1000 patient-years were 3.56 (4 / 1124) and 3.50 (6 / 1715) for control and omalizumab, respectively. The difference between both groups was similar across the groups (1.20% to 4.56% to 4.45%, respectively).

Primary malignancies in RDBPCTs

<table>
<thead>
<tr>
<th>Year</th>
<th>Omalizumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>4.3 (4 / 927)</td>
<td>4.1 (4 / 927)</td>
</tr>
<tr>
<td>2006</td>
<td>4.3 (4 / 937)</td>
<td>4.1 (4 / 937)</td>
</tr>
</tbody>
</table>

Conclusions: Previous pooled data from the omalizumab clinical trial programme showed a numerical imbalance in cancers arising in omalizumab recipients. The incidence of malignancies in the omalizumab group was similar to that expected in the general population but higher compared with control, raising a concern on the effect of omalizumab on the risk of malignancy. The difference between both groups was similar across the groups (1.20% to 4.56% to 4.45%, respectively). The incidence of malignancies in the omalizumab group was similar to that expected in the general population but higher compared with control, raising a concern on the effect of omalizumab on the risk of malignancy. The difference between both groups was similar across the groups (1.20% to 4.56% to 4.45%, respectively).

P4005
The ATTAIN study: Safety and tolerability of aclidinium bromide in chronic obstructive pulmonary disease
Eric D. Bateman1, David Singh2, Paul W. Jones3, Alvar Argüst4, Rosa Lamarca5, Gonzalo de Meaqué1, Cynthia Caracata6, Esther Garcia-Gil7, 1Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa; 2Medicines Evaluation Unit, University of Manchester, Manchester, United Kingdom; 3St George’s, University of London, London, United Kingdom; 4Thorax Institute, Hospital Clinic and CIBER Enfermedades Respiratorias and Pneumología, CIBER-Cuab-Centra, Barcelona, Spain; 5R&D Centre, Almirall, Barcelona, Spain; 6Clinical Development, Forest Research Institute, NJ, United States

Introduction: Aclidinium bromide is a long-acting muscarinic antagonist in clinical development for chronic obstructive pulmonary disease (COPD).

Aims: To assess the safety and tolerability of aclidinium 200 μg and 400 μg twice-daily (BID) in patients with COPD.

Methods: This 24-week, double-blind, Phase III study (NCT01001494) randomized patients to receive aclidinium 200 μg, 400 μg or placebo BID (1:1:1). Adverse events (AEs), clinical laboratory measures, vital signs and electrocardiograms (ECGs) were assessed.

Results: Baseline demographics were similar across all groups (safety population, N=819). The incidence of treatment-emergent AEs (TEAEs) was similar for placebo, aclidinium 200 μg and 400 μg (37.1%, 54.5%, 53.5%, respectively). COPD exacerbation was the most frequently reported TEAE in all groups (placebo, 20.5%; 200 μg, 15.9%; 400 μg, 14.1%). TEAEs reported by ≥2% of patients and with a higher incidence in the aclidinium group were: headache, nasopharyngitis, diarrhoea, cough and toothache. The incidence of TEAEs leading to discontinuation was similar across the groups (3–4%). COPD exacerbation was the most frequent reason (placebo, n=5; 200 μg, n=3; 400 μg, n=4). The incidence of anticholinergic variable AEs (≥2.5% for each group) and of general serious AEs (4–5.5% of all groups) was low in all treatment arms. Changes in laboratory tests, vital signs and ECGs were similar between groups.

Conclusions: Aclidinium 200 μg and 400 μg were well tolerated with an incidence of AEs similar to placebo. There were no differences in the safety profiles between the aclidinium dosages.

Objective: Investigate the possible relationship between the primary endpoint and previous ICS use.

Methods: Two post hoc analyses were conducted: one to determine whether children previously using different ICSs (p<0.004) were similar to placebo in response to ongoing treatment with fluticasone propionate.

Results: There was no significant difference in response to MF in 296 children previously using different ICSs (p>0.003). Most children (160; 54%) previously used FP 88–440 μg/d (median, 176 μg/d). Post hoc analysis of treatment effects in the FP subgroup determined that changes in FEV1 were similar across all groups (3–4%). No significant difference was found in the response to MF in 296 children previously using different ICSs (p=0.0372). Most children (160; 54%) previously used FP 88–440 μg/d (median, 176 μg/d). Post hoc analysis of treatment effects in the FP subgroup determined that changes in FEV1 were similar across all groups (3–4%). No significant difference was found in the response to MF in 296 children previously using different ICSs (p=0.0372). Most children (160; 54%) previously used FP 88–440 μg/d (median, 176 μg/d). Post hoc analysis of treatment effects in the FP subgroup determined that changes in FEV1 were similar across all groups (3–4%).
Background: A combination of fluticasone propionate and formoterol fumarate (FLUT/FORM; flutiform®) in a single aerosol inhaler has been developed. This study investigated the efficacy and safety of the combination compared to its individual components administered concurrently (FLUT+FORM).

Methods: Patients aged 12 years or over (N=210) with mild to moderate-severe persistent, reversible asthma were randomised in a 1:1 ratio to 12 weeks of twice daily treatment with one of two doses of FLUT/FORM or FLUT+FORM in an open-label, parallel group, multicentre study in Europe. Total daily doses were FLUT/FORM: 200/20g or 500/20g; FLUT+FORM: 200/24g or 500/24g. The primary objective was to show non-inferiority of FLUT/FORM compared to FLUT+FORM based on post-dose forced expiratory volume in 1 second (FEV₁) on Day 84.

Results: FLUT/FORM had comparable efficacy to FLUT+FORM in the treatment of asthma with mean FEV₁, 30 to 60 minutes post-dose on Day 84 of 2.6L in both groups (per protocol groups; least squares mean difference: -0.03 L; 95%CI: -0.148, 0.081; p=0.004). The lower limit of the 95% CI was above the pre-defined non-inferiority threshold of \( \geq -0.2 \). Analysis of other pulmonary function tests, patient reported outcomes, rescue medication use, asthma exacerbations and quality of life questionnaires were also comparable. The safety profiles of the two study groups were similar overall.

Conclusions: Fluticasone/formoterol combination therapy has comparable efficacy to its individual components administered concurrently. The safety and tolerability profile of fluticasone/formoterol combination therapy is similar to that of its individual components.

P4008

Body mass index, disease control and airway inflammation in asthmatic patients

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Background: The association between overweight and asthma remains controversial.

Aim: To investigate the relationship between body mass index (BMI), disease control and airway inflammation in an asthmatic population.

Methods: We consecutively studied 408 patients (43±16 yr; 248 F). In all patients, BMI, spirometry, Asthma Control Test (ACT) and Fractional Exhaled Nitric Oxide (FeNO, ppb) were measured.

Results: 205 patients had a BMI > 25 kg/m² and, as compared to those with normal BMI, had lower values of FVC, FEV₁, FEV₁/FVC, FEF₂₅, FEF₂₅ and FEF₇₅ (p<0.05 for each comparison). The ratio between the mean values of the patients with controlled asthma (ACT ≥ 20) and that of patients with poor controlled asthma (ACT < 20) was significantly lower in patients with increased BMI (106/99 vs 131/71; \( r² = 7.227, p<0.01 \)). In patients with increased BMI, the odds ratio of uncontrolled asthma was 1.723 (95% CI = 1.157-2.566). No difference was observed in FeNO values between the two groups of patients.

Conclusions: Our results show that in an asthmatic population, the increase in BMI is associated with poor spirometry and worse disease control, but not with FeNO values.

P4009

How does obesity correlate with severe asthma?

David Gibbons, Winston Banyan, Hofmann Markus, Regan Suzanne, Pankaj Bhavsar, Kian Fan Chung, Andrew Menzies-Gow. University Hospital of Parma, Parma, Italy

Introduction: 10% of asthmatics have refractory disease. Cluster analysis has identified that BMI is a factor in defining phenotypes of severe asthma [1]. Obesity antedates asthma diagnosis [2], suggesting that obesity has a pathophysiological role.

Last year we reported the outcome of 115 patients with severe, treatment refractory asthma (ATS, 2000). This study looks at data from 374 patients from 4 UK centres, collected as part of the National Registry for dedicated UK Difficult Asthma Services.

Methods: Patients were divided into three groups by BMI: 18.5 to 24.9, 25 to 29.9 (overweight), and ≥30 (obese).

Results: The table below highlights demographic data, lung function, steroid use and bone density between groups.

Conclusion: Severe asthmatics are more likely to be female although this does not appear to correlate to BMI. Raised BMI is associated with more GORD, greater use of PPI’s, increased KCO, but a reduction in aspirin sensitivity, and appears to be protective against osteoporosis at the neck of femur.


P4010

Effects on adrenal function of a new combination of fluticasone propionate/formoterol fumarate administered to asthmatic patients and healthy subjects

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Background: Corticosteroid treatment is known to affect adrenal function via suppression of the hypothalamic-pituitary-adrenal axis. This effect was assessed for a new asthma therapy combining the corticosteroid fluticasone (FLUT) with formoterol (FORM) in a single aerosol inhaler (FLUT/FORM; flutiform®).

Methods: Healthy subjects and patients with mild to severe asthma were treated for 4 to 12 weeks with FLUT/FORM (100/10g, 250/10g, or 500/20g b.i.d.) in 3 randomised, parallel-group studies comparing FLUT/FORM with FLUT, FLUT+FORM from separate inhalers, or placebo. The endpoints were changes in urinary and serum cortisol levels from baseline to end of study.

Results: No significant differences were observed in mean urinary cortisol levels with FLUT/FORM 100/10g (N=38; mean 21.51μg/24h; p=0.733) or FLUT/FORM 250/10g (N=40; mean 24.01μg/24h; p=0.510) compared with placebo (N=39; mean 21.95μg/24h). In a study using FLUT/FORM 100/10g or 250/10g, patients had similar mean urinary cortisol levels at baseline and end of study (N=27; 5.1 vs 6.1nmol/L). The corresponding mean serum cortisol levels were 372.9 vs 412.6nmol/L (N=104). Healthy subjects given FLUT/FORM 500/20g had a decrease in both urinary and serum cortisol levels at end of study but this was less than with FLUT 500/2g+FORM 24g (urinary: N=24; 13 to 7 to 10 nmol/L; serum: N=24; 399 to 272nmol/L vs 430 to 154nmol/L).

Conclusions: Fluticasone/formoterol 100/10g or 250/10g showed no significant changes in urinary or serum cortisol levels. Fluticasone/formoterol 500/20g had some effect on adrenal function but less than FLUT+FORM given at the same nominal dose.

416. Update on monitoring airway diseases

P4011

WITHDRAWN
P4012 Assessing the burden of asthma and COPD in Salford UK: Retrospective analysis using a whole population electronic medical record
John New1, Mark Delderfield1, Norman Stein1, Stephanie Austin1, Jorgen Vobso1, Ashley Woodcock2, North West e-Health, Salford Royal NHS Trust, Salford, United Kingdom; 2Manchester Academic Health Sciences Centre, University Hospital of South Manchester, Manchester, United Kingdom; 3School of Translational Medicine, University Hospital of South Manchester, Manchester, United Kingdom

There is limited information on predictors of disease progression and their association with managing asthma and COPD in primary care. This retrospective, real-life, observational cohort study used an electronic medical record (EMR, all residents in Salford) to evaluate patient characteristics and health resource utilisation in asthma and/or COPD patients ≥18 years of age. The study included an open cohort of 180,493 adults ≥18 years, the prevalence of asthma was 4.4% of COPD 2.5%. Most commonly prescribed controller medications were: EMR, Asthma: ICS 42%, LABA 40%; COPD: ICS and LABA 56%, LAMA 36%. Resource utilisation was greatest in patients with a history of exacerbations in 2008:

12 month resource utilisation data per 100 person-years during 2009, subsets predefined from data during 2008

<table>
<thead>
<tr>
<th>Asthma COPD</th>
<th>Mean Age (yrs)</th>
<th>47.6</th>
<th>68.0</th>
<th>Mean FEV1 (%)</th>
<th>86.0</th>
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<tr>
<td>Subtotal</td>
<td>109.1</td>
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<td>190.7</td>
<td>125.3</td>
<td>179.6</td>
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<td>ICS/LABA</td>
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<td>1702.5</td>
<td>1526.0</td>
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<td>≥1 exacerbation</td>
<td>34.7</td>
<td>10.1</td>
<td>244.1</td>
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<td>Antibiotics</td>
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<td>GP visits – all (routine and unscheduled)</td>
<td>1068.9</td>
<td>1325.0</td>
<td>1097.2</td>
<td>1253.0</td>
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<td>23.3</td>
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<td>Hospitalisations – respiratory cause</td>
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<td>4.7</td>
<td>2.9</td>
<td>13.6</td>
<td>17.2</td>
<td>16.6</td>
</tr>
<tr>
<td>Short courses oral steroids</td>
<td>34.7</td>
<td>10.1</td>
<td>38.5</td>
<td>244.1</td>
<td>244.1</td>
<td>244.1</td>
</tr>
<tr>
<td>Total</td>
<td>109.1</td>
<td>8.5</td>
<td>190.7</td>
<td>125.3</td>
<td>179.6</td>
<td>141.8</td>
</tr>
</tbody>
</table>

Conclusions:
- EMR collected during routine clinical care can quantify the burden of asthma/COPD.
- EMR can identify exacerbations (oral steroids/antibiotics or hospitalisation).
- EMR could evaluate differences in disease outcomes with novel treatments.

P4013 Lipid peroxidation products-diagnostic utility in differentiation of pleural effusions
Jasna Lalic1, Ivan Lalic1, Ivanka Djordjevic2, Milanka Ljubenovic1,1 Centre of Medical Biochemistry, 2Clinic for Lung Diseases, Clinical Centre, Nis, Serbia

Introduction: Biochemical analysis of pleural fluid are the first step in differentiation of pleural effusions (PE) into exudates (E) and transudates (T). Therefore, new parameters have been used to improve the accuracy of diagnosis. Free oxygen radicals (FOR) are known to produce damage in many biological tissues. FOR exert their cytotoxic effect by causing lipid peroxidation which is believed to be responsible for the exudation of fluid into the pleural space.

Aims: Based on this idea, the aim of this study was the determination of malondialdehyde (MDA), as the final product of lipid peroxidation in pleural fluid (MDAP) and in serum (MDAs) and pleural fluid to serum MDA ratio (MDAPvs); and to compare our results with other well established criteria.

Methods: We analysed 52 patients with PE who were classified as E(32) and T(20) by Light’s criteria. MDA was measured by spectrophotometric method with TBA. Results: Our results showed significant increase of MDAs level in both groups of patients: E (7.7±1.29 μmol/L) and T (7.75±0.89 μmol/L) in comparison with control group (5.10±0.87 μmol/L) p<0.001. MDAP level in E (5.16±1.28 μmol/L) was also significantly increased than in T (2.67±0.61 μmol/L), p<0.001. Similarly, MDAPs ratio was significantly higher in E (0.72±0.17 μmol/L) than in T (0.34±0.05 μmol/L); p<0.001. Using a cut-off value (0.4) for MDAPs ratio (sensitivity 95% and specificity 90%) effectively separated E from T.

Conclusion: Based on these results we can conclude that determination of lipid peroxidation products may be useful in diagnosis-differentiation of pleural effusions into E and T. It is of significance for the correct treatment of patients.

P4014 Challenge already established: Identification of risk factors for early need for ventilatory support in Duchenne muscular dystrophy
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Introduction: Duchenne muscular dystrophy (DMD) is a genetic, progressive and disabling disease. Functionally, it puts a restrictive respiratory disorder. Faced with signs and symptoms of chronic respiratory failure should be started as ventilatory support (VS), usually in the second half of adolescence, which was initially due to nocturnal hyperventilation. Ventilair Program (VP) assist DMD patients VS-users and VS-non users in John Paul II Child Hospital/Hospital Foundation of Minas Gerais State (IPJCH/HFHEMIG).

Objective: To identify among patients with DMD assisted by the VP/PIPC/ HFHEMIG, possible risk factors for the need early VS.

Patients and methods: Cohort study between 2002-2010. Clinical score 20 points to 1 point for each sign of hyperventilation. Risk factors associated with VS were evaluated in multivariate analysis by proportional hazards model of Cox. Multivariate model of Cox: all variables p<0.20 in univariate analysis. Final level of significance p<0.05. Group A: 16 (23.8%) VS-users; group B: 46 (74.2%) VS-non-users. Group C: loss of ambulation before 10 years and group B after 10 years. Results: Statistically significant difference in univariate analysis for risk factors: body mass index: p=0.15, difficulty swallowing (p=0.05), moderate to severe scoliosis (p=0.01), age at loss of ambulation (p<0.001) and clinical score 0.17 and >17 points (p<0.001). Cox final model: clinical score: relative risk 1.89 (p=0.001) and loss of ambulation before 10 years: relative risk 2.04 (p=0.01).

Conclusion: Age at loss of ambulation and clinical score were independent risk factors for the installation of VS before 20 years of age of DMD patients.

P4015 ISAAC Malta: Changes in geographical distribution of wheezing children in Malta between 1994 and 2002
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Introduction: Malta is one of the centres which participated in the Phase 1 and 3 of The International Study of Asthma and Allergies in Childhood (ISAAC).

Aim: To investigate changes in the geographical distribution of wheezing in the Maltese Islands.

Methods: ISAAC Malta Phase 1 was carried out in 1994 with 3506 participants from 24 schools for the 5 to 8 year old age group and 4184 participants from 25 schools for the 13 to 15 year old age group.

ISAAC Malta Phase 3 in 2001 studied 3800 from 44 schools and 4139 children from 18 schools in the 5 to 8 and 13 to 15 year old age groups respectively.

Results: In the younger age group there was an increase from 8.8% to 14.8% (p<0.00001) in the total prevalence of current wheezing between 1994 and 2001. Most geographical regions of the Maltese islands reported an increase in wheezing with the Central East (10.2% vs 23% p<0.00001), Grand Harbour (8.5% vs 21.2% p<0.0005), East (8.6% vs 22.5% p<0.00001) and Central North (6.5% vs 16.3% p<0.0004) regions having the largest increases. The prevalence of current wheezing in the older age group remained stable (16% to 14.6% p=0.08). A decline in current wheezing (p=0.5) was observed in Central West (16.3% vs 11.2%), West (17.5% vs 12.6%) and South (14.8% vs 11.2%) while three regions reported an increase in wheezing.

Conclusions: A strong genetic component together with environmental factors must influence the geographical distribution of wheezing in the Maltese Islands.

P4016 The relationship between sleep respiratory disorder and daytime PaO2 in OSAS and in overlap syndrome
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OSAS and COPD are often associated with daytime hypoxemia. Overlap Syndrome (OS) increases the risk of daytime hypoxemia. The aim of this study was to investigate the mechanisms which could justify the low oxygen’s level in these patients and the effect of CPAP therapy.
Background: Oxygen is one of the most commonly used drugs in a hospital setting. National and International Thoracic Society guidelines recommend improvement of oxygen use in hospital settings aimed at standardising practice in the setting. The British Thoracic Society (BTS) published guidelines in Oct 2008 that advocated for the use of CPAP therapy in the hospital setting to guide oxygen use and delivery of oxygen therapy. An audit was carried out in 2010 in East Kent Hospitals University Trust (EKHUT) to assess current practice of prescription and use. In total 740 patients were audited.

Methods: Surveys were given to staff as part of a discharge questionnaire and medical notes were used to gather information about oxygen prescription and use. In total 740 patients were audited.

Results: 11% of patients in EKHUT were using oxygen at the time of the audit. This is comparable with national figures of 17.5%. Only 30% had formal prescription and use. In total 740 patients were audited. 11% of patients in EKHUT were using oxygen at the time of the audit. This is comparable with national figures of 17.5%. Only 30% had formal prescription and use. In total 740 patients were audited.

Conclusion: This audit has highlighted the need to raise awareness in all medical and nursing staff of BTS recommendations and educate health professionals to deliver oxygen in a more standardised and safe manner.

P4018
Computed tomography of the chest as a way to diagnose and monitor treatment of patients with sarcoidosis in Omsk, Russian Federation
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Purpose: To evaluate lung injuries with computed tomography (CT) for diagnosis and therapeutic follow-up of patients with sarcoidosis (S).

Methods: 247 consecutive patients with biopsy-proven S were retrospectively included respectively. All patients underwent chest CT scan (CS) twice. Current asthma control and CS were re-examined by CT to assess response to CS treatment at 3 and 6 months.

Results: 563 consecutive OSAS patients were enrolled. According to pulmonary function test they were divided in 2 groups. Group 1: 473 OSAS/COPO+/-; Group 2: 90 patients OSAS/COPO+/. All patients underwent blood gases, nocturnal polysomnography, post-bronchodilator spirometry. A multivariate analysis was performed to evaluate which were the factors that determined the diurnal PaO2. The groups were matched for BMI, for age and AHI. OS group showed lower level of daytime PaO2 compared with OSAS patients (71±6.9 to 79.3±11 mmHg, p<0.001), the alveolar-to-arterial oxygen partial pressure difference (AaDO2) was higher in OS than in OSAS (28.3±9 vs 22.6±7 mmHg, p<0.05), the TST90 was higher in OS (34.8±35.5 vs 24%±26). In OS group diurnal PaO2 correlated with age (coef=0.41) with AHI (0.18) and with FEV1 (0.21), while in OSAS group the correlation was found with age (coef=0.27), FEV1 (0.07) and mostly with BMI (0.46), but not with AHI. In both groups, patients with good compliance (~48% of time) of CPAP improve daytime PaO2 (p<0.001) whereas, in patients with poor compliance PaO2 was reduced (p<0.001).

Our data suggest that daytime hypoxemia in OSAS patients is largely determined by the increased weight of body. In the overlap patients daytime hypoxemia has a more complex origin. However CPAP therapy has been shown to improve daytime PaO2 values both in OSAS than in OS patients with good compliance.

P4019
Ventilation heterogeneity is associated with asthma control in adults
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1 Woolcock Institute of Medical Research, University of Sydney, Sydney; 2 CRCAA, Co-operative Research Centre for Asthma and Airways, Glebe, 3 Dept of Respiratory Medicine, Royal North Shore Hospital, Sydney, Australia

Background: The clinical relevance of increased ventilation heterogeneity, a marker of small airways damage in asthma is unclear. Ventilation heterogeneity is an independent determinant of airway hyperresponsiveness, improves with bronchodilators and inhaler corticosteroids (ICS), and worsens during exacerbations but its relationship to asthma control is unknown.

Objective: To determine the association between ventilation heterogeneity and current asthma control before and after ICS treatment.

Methods: Asthmatic subjects had the 5-item symptom-only asthma control questions (ACQ) and lung function measured at baseline and after 3 months of high dose ICS treatment. Ventilation heterogeneity was measured as Scond and Sacin by multiple breath nitrogen washout. Scond and Sacin represent ventilation heterogeneities in small airways where gas transport occurs mainly by convection or diffusion, respectively. Spearman correlations and paired t-tests were performed.

Results: At baseline (n=110, 64 female), ACQs correlated with Scond (r=0.30, p=0.002) and with Sacin (r=0.21, p=0.03). After treatment (n=55), the mean (SD) ACQs improved (1.31 (0.71) to 0.76 (0.77), p<0.0001), Scond improved (0.068 (0.035) to 0.053 (0.033) L1, p<0.0001) but Sacin did not significantly change (0.147 (0.07) to 0.142 (0.06) L1, p=0.28). The change in ACQs correlated with changes in Scond (r=0.34, p=0.02) and in Sacin (r=0.33, p=0.01).

Conclusions: Current asthma control is associated with markers of small airways disease. Improvements in ventilation heterogeneity with anti-inflammatory therapy are associated with improvements in symptoms. Sensitive measures of small airways function may be useful in monitoring therapy in asthma.
Methods: Data for the first 67 patients to undergo FENO testing with NOX MINO in a secondary care adult asthma clinic were collected. ICS doses are expressed as mean ± SD daily beclomethasone equivalent.

Results: FENO was performed in 17 patients undergoing diagnostic workup for asthma. The need for histamine challenge testing was prevented in 10 patients with normal spirometry and FENO; six patients were subsequently discharged who would otherwise have required follow-up. Of the 50 patients with persistent asthma, receiving ICS, FENO was high (>45 ppb) in 15, intermediate (25–45 ppb) in 8 and normal (<25 ppb) in 27. FENO altered decision-making in 22 (44%) patients by permitting a reduction (n=5) or maintenance (n=12) in ICS in patients who would otherwise have had their dose increased, and a reduction in 7 patients who would have had their ICS dose maintained. There was more appropriate matching of ICS dose changes to FENO, with a reduction in ICS dose in patients with normal FENO (164±9.87µg to 138.1±92.6 µg; p=0.017), with no change in the intermediate FENO group (1738±639 µg to 1800±513 µg; p=0.35), and an increased dose in the high FENO group (2140±767 µg to 2733±683 µg; p=0.007).

Conclusions: In almost half of patients tested, FENO prevented the need for a bronchial challenge testing in patients undergoing diagnostic workup for asthma and permitted reduction in overall steroid burden in patients receiving ICS contraception. This approach will be followed to see what effect FENO has on overall asthma control and steroid dose burden.

P4022 Functional, clinical evolution and cellular inflammatory pattern in induced sputum in patients with difficult-to-control asthma

Background: Patients with difficult-to-control asthma (DCA), show several phenotypes. Our aim is to identify phenotypic modifications over time in this population.

Materials and methods: Prospective study in subjects with DCA. Clinical status was evaluated by Asthma Control Test (ACT), exacerbations/6 months (E6M) and relief therapy use (RTU). Daily corticosteroids dose (inhaled -ICs- or oral -OCs-) was calculated as the average of the last 6 months. Treatment was titrated to achieve the lowest possible dose. Patients were followed up for 6 months. Results: 26 patients with DCA were enrolled. Outcomes at initial time (T0): ACT 15 (6), E6M 1.8±1.0, RTU 1.2±0.8. Day 6 months (T6): 2 patients improved ACT in three or more points. The patients improve ACT had a paucigranulocytic pattern. Patients with similar or poor ACT had an eosinophilic pattern in sputum. At T0 microorganisms were isolated in 2 of 3 patients with controlled asthma and after 6 months the bacterial cultures were negatives but the inflammatory pattern in sputum changed to paucigranulocytic form. In 2 patients with uncontrolled asthma were observed MP and their pattern changed to mixed form at T6.

Conclusions: 50% patients with DCA who improved their ACT on 6 months, show a paucigranulocytic pattern in sputum. Patients who didn’t improve showed aggressive patterns (eosinophilic, neutrophilic and mixed). There are individualized changes to benign or aggressive patterns in sputum without improvement or worsening expected in ACT. Some patients had microbial colonization associated with aggressive patterns in sputum.

P4023 Relationship between circulating TH2 prevalence and asthma control in pregnant asthmatics

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Introduction: Asthma is one of the most common diseases complicating pregnancy and a risk factor for several maternal and fetal complications. It was previously shown that altered systemic inflammation present in pregnant asthmatics may contribute to the outcome of the pregnancy; however less has been known about the relationship between circulating T cell profiles and clinical characteristics of asthma in pregnant patients.

Aim: The aim of this study was to assess the relationship between various T cell profiles and clinical variables in asthma during gestation, including lung function, exhaled nitric oxide, and asthma control.

Methods: The prevalence of TH1, TH2, and Treg lymphocyte subsets was identified by cell surface markers and intracellular FoxP3 staining in 22 pregnant women in the second or third trimester suffering from persistent allergic asthma. FENO, Asthma Control Test (ACT) total score and lung function were also evaluated.

Results: A positive relationship was observed between TH2 cell prevalence and FENO in 21 (69%) of the 30 patients tested. The relationship was not observed between TH2 cell prevalence and ACT total score (<0.48, p=0.03), while no relationship was found between TH2 prevalence and FENO or lung function parameters. However, none of the other T cell subsets were correlated to any of the clinical characteristics (FENO, lung function, or ACT; p>0.05).

Conclusions: The level of asthma control related to blood TH2 cell prevalence suggests a direct relationship between symptoms and cellular mechanisms of asthma in pregnant patients.

The study was supported by OTKA 68808.

P4024 Chronius: A new wearable monitoring system for COPD patients

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CHRONIOUS is a FP7 European Community project which also includes a new wearable platform for home monitoring of people suffering from chronic diseases. The wearable system is composed of a shirt made of washable stretch-material into which are sewn 4 ECG electrodes, two bands for respiratory inductive plethysmography (RIP) and a reflectance pulseoximeter. The data coming from the sensors are collected and transmitted via wireless connection by the Data Handler, a microcontroller-based acquisition system. To evaluate accuracy and usability of this device, we studied 9 COPD patients (70±8±6 years, FEVI 45±1±9%pred) during 1 hour in the seated and 1 hour in the supine positions.

Methods: Breathing spontaneously and data were collected continuously. At the beginning and at the end of each hour flow at the mouth was also measured by a spirometer (Sibelmed, Barcelona, Spain), heart rate (HR) and oxygen saturation (SpO2) by a finger clip pulseoximeter (NONIN, Plymouth, Minnesota, USA) for 10 minutes, to get reference values for comparison. The first measurement for each subject with the spirometer was used to calibrate the RIP using Sackner algorithm, J.Appl.Physiol.1989; 66(1): 410-420.

The evaluation of accuracy was focused on the following parameters: HR, SpO2 and tidal volume (VT). Linear regression analysis on the data acquired resulted as follows: HR r=0.99, m=1.00, q=0.31, SpO2 r=0.92, m=1.29, q=-27.54, VT r=0.89, m=1.15, q=0.07.2. From the signals of the ECG electrodes it was possible to identify PQRST waves within the 3rd derivations.

The new wearable monitoring system provided reliable measurements of HR, SpO2, VT and ECG in both supine and seated posture. RIP calibration was still consistent after 1 hour of use.

P4025 Using routine spirometry to obtain sputum samples in the respiratory laboratory

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Background: Analysis of sputum is helpful in diagnosis and management. Not all patients present sputum on request. However most under spirometry during their clinic visit. We had noticed that many patients asked for a sputum sample during spirometry which has often swallowed and wondered if this might be an opportunity to obtain a sample.

Methods: 303 consecutive patients performing nurse led spirometry in our chest clinic at the North Bristol Lung Centre from 1st November 2010 to 31st January 2011 were studied. Initial 139 patients were not informed prior to spirometry that a sputum specimen was required; subsequent 164 patients were asked to provide a specimen if possible. Nature of the sputum (mucoid/purulent) was recorded by the nurse.

Results: Of the initial 139 patients, 14 (10%) produced sputum spontaneously 19 (12)%of the subsequent 164 were able to produce sputum on request during spirometry. Many patients in both groups swallowed sputum during spirometry. Among the 303 patients, 66 (22%) had bronchiectasis, 65 (21%) had asthma and 53 (18%) had chronic obstructive pulmonary disease (COPD). Among those who produced sputum at spirometry, 22 (17) had bronchiectasis, 5 had COPD and 4 asthma.

22/33 sputum samples collected were sent to the laboratory. Sputum assessment by the clinic nursing staff matched that of the lab in 18 (82%) of the 22 cases.

Conclusion: Performing spirometry provides an opportunity to gain sputum. Forewarning the patient appears to have no effect on giving a sputum specimen. Nurses' categorisation of sputum nature correlates well with microbiology laboratory assessment. Categorisation as mucoid may enable fewer samples to be submitted for microbiology assessment.

P4026 Concordance between the new questionnaires to evaluate asthma control

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Objectives: Regarding asthma, the main objective is to control the disease symptoms. Both Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) are one of the most used tools to evaluate asthma control in medical practice. Two studies have been recently published where new cut-off points for ACT (> 21, 19-20) and ACQ (>0.5), from 0.6 to 0.9 and -1) are established. This led us to evaluate the concordance between both test in our patients.

Methods: We have included 179 asthmatic patients chosen from our medical practice, who performed both questionnaires and were classified in different categories of asthma control, and we analyzed the concordance of the results.

Results: The average age of our patients was 45±6 years and the FEVI measured was 2.6±0.9 litres (82±22%).
The classification of our patients, according to the questionnaires is shown in Table 1.

Table 1. Asthma control evaluation according to specific questionnaires

<table>
<thead>
<tr>
<th>ACT (&lt;20, 18-19, &lt;18)</th>
<th>Control</th>
<th>Partial Control</th>
<th>No Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT (&gt;=20, 18-19, &lt;18)</td>
<td>60 (33.17%)</td>
<td>31 (17.32%)</td>
<td>88 (49.16%)</td>
</tr>
<tr>
<td>ACQ (&lt;0.5, 0.6-0.9, &lt;1)</td>
<td>43 (18.53%)</td>
<td>19 (8.20%)</td>
<td>113 (48.70%)</td>
</tr>
</tbody>
</table>

By comparing the results of both questionnaires, we find a very good correlation (correlation coefficient 0.75) and a poor concordance (kappa 0.556), although statistically significant (p < 0.001).

**Conclusions:** As we cannot find a good concordance between both questionnaires it is not possible to exchange them or their cut-off points, so it would be convenient to carry out prospective multicentre studies using both questionnaires and GINA/GEMA criteria.

**P4027**

Data reduction for large scale cough studies using distribution of audio frequency content

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**Background:** Recent studies have suggested that the objective quantification of coughing from sound recordings provides novel insights into the mechanisms underlying cough and the efficacy of therapies. However, reliable methods for minimizing the large sound data are required to improve the feasibility of processing many and large patient data records for large scale studies of cough treatments for both manual and potential automatic cough counting.

**Aim:** To determine if a developed system can identify periods of inactivity in sound recordings to significantly reduce record length without degrading data (i.e. inadvertent removal of cough sounds), referred to hereafter as destructiveness.

**Methods:** Inactive periods of audio are identified by measuring the median audio frequency within small segments of recordings and removing those below a selected threshold. 200 randomly selected 15 minute periods known to contain cough, from 20 patients [healthy (5), COPD (5), asthma (5) and chronic cough (5)] were used, each recorded for 24hrs. To measure destructiveness, both the audio kept and removed by the algorithm were analysed by trained cough counters and compared to counts for the original files. Finally, the efficacy of the algorithm was determined by the reduction in record length achieved across all of the patient data.

**Results:** The average resultant file size was 6.04% (54.4s) of the original (median 5.77% of the original). The average resultant file size was statistically significant (p < 0.05).

**Conclusions:** The system has shown to be reliable for use in cough monitoring as an excellent means of removing large sections of audio and profoundly improving the efficiency of manual cough counting.

**P4028**

Oropharyngeal pH evaluation to determine the presence of airway reflux in asthmatic patients

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**Introduction:** Reflux disease can affect the tracheobronchial tree directly, this has been led to as先导 pathophysiology of asthma. Currently pharyngeal pH measuring detects only liquid reflux.

**Aims and objectives:** To evaluate the presence of gaseous reflux in pharynx by the comparison of the signal path of the EGRF with the cascade of MAP. This method of regulation is used in the cells of respiratory epithelium as a response to the impact of air pollutants and caused in the inhibition of apoptosis in pathogenesis of COPD Low-molecular-weight, nucleosomal DNA fraction (lmwDNA) of the blood plasma is an universal quantitative indicator of apoptosis, which allows to distinguish fundamentally different condition of the organism. The states connected with the apoptosis inhibition. The COPD is noticed for the first time accompanied by strengthening of apoptosis are marked by increase in lmwDNAs fraction. The COPD is noticed for the first time accompanied by strengthening of apoptosis are marked by increase in lmwDNAs fraction. The COPD is noticed for the first time accompanied by strengthening of apoptosis are marked by increase in lmwDNAs fraction. The COPD is noticed for the first time accompanied by strengthening of apoptosis are marked by increase in lmwDNAs fraction. The COPD is noticed for the first time accompanied by strengthening of apoptosis are marked by increase in lmwDNAs fraction.

**Results:** The expression of the protein Ras is the basis of the activation of cell cycle by the connection of the signal path of the EGFR with the cascade of MAP. This method of regulation is used in the cells of respiratory epithelium as a response to the impact of air pollutants and caused in the inhibition of apoptosis in pathogenesis of COPD. Low-molecular-weight, nucleosomal DNA fraction (lmwDNA) of the blood plasma is an universal quantitative indicator of apoptosis, which allows to distinguish fundamentally different condition of the organism. The states connected with the apoptosis inhibition. The COPD is noticed for the first time by the decline of the level of lmwDNA in the blood plasma unlike in the case of the COPD patients. COPD patients in the remission state the lmwDNA level consisted 7.8 ng/ml plasma (n=31) and was lower (P < 0.05) than in non-COPD patients - 28.0 ng/ml (n=22). Our results suggest with the dates of the detection of K-ras mutation in plasma DNA. It is used as a method of determination of malignant disease and risk factor for them. The results indicate that is it possible to use the proposed indicator for integrated differential diagnosis in practical medicine. Further research in this field is promising.

**P4029**

Comparison of the asthma control test and % predicted FEV1 in relation to correlation with physicians assessment of asthma control and treatment decisions

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**Background:** The Asthma Control Test (ACT) is a 5-item questionnaire for the assessment of asthma control. An ACT score of <20 correlates with poorly controlled asthma.

This study compared whether ACT or FEV1 correlated better with physicians assessments of asthma control and treatment decisions made by clinicians.

**Method:** Serial visits were reviewed to a specialist Asthma Outpatients Clinic. All subjects completed the Asthma Control Test and performed same day spirometry. Clinicians made their own assessment of the patients’ asthma control and made appropriate treatment decisions. The clinicians were not blinded to the results of spirometry or ACT.

**Results:**

<table>
<thead>
<tr>
<th>ACT</th>
<th>FEV1 &lt; 0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26 96 57 65</td>
</tr>
<tr>
<td>Mean age</td>
<td>48 47</td>
</tr>
<tr>
<td>Mean % FEV1</td>
<td>93.7 73.7 103.4 58.1</td>
</tr>
<tr>
<td>Physician Judged Controlled (%)</td>
<td>88.4 24.2 53.6</td>
</tr>
<tr>
<td>Physician Judged Uncontrolled (%)</td>
<td>11.6 75.8 46.4 75.4</td>
</tr>
<tr>
<td>Treatment Increased (%)</td>
<td>3 38.5 21.4 42.4</td>
</tr>
<tr>
<td>Treatment Unchanged (%)</td>
<td>85.6 57.3 75.1 54.5</td>
</tr>
<tr>
<td>Treatment Decreased (%)</td>
<td>15.4 4.2 7.1 6.1</td>
</tr>
</tbody>
</table>

In the group defined as having controlled asthma (as defined by ACT < 20), 88.4% of patients were also classified as controlled by clinicians. However, in the group with % predicted FEV1 < 0.8, only 53.7% of patients were classified as controlled by clinicians.

**Conclusion:** The results of our study show that an ACT score < 20 had a strong association with the physicians assessment of asthma control and correlated better with treatment decisions than did the severity of asthma as defined by FEV1. The ACT could serve as a useful in the assessment and management of asthma by guiding physicians with regards to asthma control.

**P4030**

Circulating nucleosomal DNA of blood as an indicator of the pathological process during chronic bronchitis

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The expression of the protein Ras is the basis of the activation of cell cycle by the connection of the signal path of the EGFR with the cascade of MAP. This method of regulation is used in the cells of respiratory epithelium as a response to the impact of air pollutants and caused in the inhibition of apoptosis in pathogenesis of COPD. Low-molecular-weight, nucleosomal DNA fraction (lmwDNA) of the blood plasma is an universal quantitative indicator of apoptosis, which allows to distinguish fundamentally different condition of the organism. The states connected with the apoptosis inhibition. The COPD is noticed for the first time by the decline of the level of lmwDNA in the blood plasma unlike in the case of the COPD patients. COPD patients in the remission state the lmwDNA level consisted 7.8 ng/ml plasma (n=31) and was lower (P < 0.05) than in non-COPD patients - 22.5 ng/ml (n=22). Assumption about the inheritability of this index was made. The mean values of lmwDNA in the group of healthy first-degree relatives of COPD patients compound 32.9 ng/ml (n=19) and it is 1.24 time lower than in group of relatives of non-COPD patients - 28.0 ng/ml (n=22). Our results suggest with the dates of the detection of K-ras mutation in plasma DNA. It is used as a method of determination of malignant disease and risk factor for them. The results indicate that is it possible to use the proposed indicator for integrated differential diagnosis in practical medicine. Further research in this field is promising.

**417. Bronchial hyperresponsiveness and exhaled and sputum biomarkers**

**P4031**

Efficiency of a laser-based sensor for FeNO measurements and multiple flows analysis

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The system has shown to be reliable for use in cough monitoring as an excellent means of removing large sections of audio and profoundly improving the efficiency of manual cough counting.

**Aims and objectives:** To evaluate the presence of gaseous airway reflux in physiologic asthmatic patients, utilising the “Dr-pH Measurement System” (Restech, Respiratory Technology Corporation, San Diego, California, USA). The Dr-pH probe can detect the pH of aerosolized droplets and liquid.

**Methods:** Asthmatic patients with symptoms assessed on the Hull Airway Reflux Questionnaire (HARQ) underwent 24-hour airway pH monitoring with the Dr-pH measurement system. The probe was inserted transnasally in to the oropharynx with the distal end sitting lateral to the uvula. A Ryan score (composite pH score for pharyngeal acid exposure) was calculated for both the upright and supine periods.

**Results:** The study population consisted of 12 asthmatic patients (1 male, 11 female) with a mean age of 50 range (33 - 72). Ryan score values for the upright period were 2.12 - 612.57 (normal <9.41) and for the supine period were 2.17 - 38.01 (normal <6.80). The mean HARQ score was 32/70. Airway reflux was present, confirmed by an abnormal Ryan score in 75% of the study population in the upright position and 58% in the supine position.

**Conclusion:** Airway reflux is a frequent condition in asthma patients. It should be recognised as a distinct entity that warrants specialized focus and treatment to improve the symptoms of patients suffering with exoasthmopage reflux and asthma. The Dr-pH probe is a useful diagnostic tool for patients with asthma and symptoms suggestive of airway reflux.

**735s**
Fractional exhaled nitric oxide (FeNO) is a useful indicator in the diagnostic and management of asthma in children. Up to now, despite the availability of standardized recommendations, numerous wavelengths and several NO sensors have been reported. The aims of this study were to compare different analyzers by measuring the FeNO in asthmatic children and to calculate the NO parameters in healthy people by using NO sampling at various expiratory flow rates. A laser-based sensor with sub-ppb (sub-part-per-billion by volume) detection limit [1] was compared with two market sensors; a chemiluminescent analyzer (model 280, Sievers) and a portable hand-held electrochemical analyzer (MINGO®, Aero-crime AB), respectively. FeNO from 20 children (6-16 years of age) diagnosed with asthma and treated with inhaled steroid was simultaneously measured with these devices. The data analysis was used to validate the accuracy, precision, sensitivity and reproducibility of the optical sensor. The finding shows that FeNO values are comparable between the different analyzers. However, the variability of the electrochemical-catalytic analyzer should be considered for clinical decisions as changing current treatment.

In AR patients treated by nasal corticosteroids and antihistamines in the season deficiency and usual COPD depressed suspicious inflammation in the lower airways. This study has shown that patients with AR have significantly higher eNO levels in AR patients outside the season (14.2 ppb; IQR=13.38) and in the season before treatment (23.15 ppb; IQR=16.63). No difference was found in the pollen season after treatment (16.1 ppb; IQR=15.6).

**Reference:**


**P4032**

The impact of diurnal variations, atopy, pollen exposure and pharmacotherapy on exhaled nitric oxide levels Alica Bencova, Martina Antosova, Eva Rozbovtova. *Clinic of Pneumology and Phthisology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia (Slovak Republic); 2Institute of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia (Slovak Republic)

Objectives and aims: The aim of the study was to investigate the impact of diurnal variations in healthy subjects and impact of atopy, pollen exposure and pharmacological treatment on exhaled nitric oxide levels (eNO) in patients with allergic rhinitis (AR).

**Methods:** eNO levels were measured using analyzer NIOX. Measurements of eNO were performed in 81 nonasthmatics with seasonal AR outside and during the pollen season, before and 3 weeks after treatment and in 52 healthy controls in 4-hour intervals.

**Results:** Diurnal variations of eNO in healthy individuals were not confirmed. Patients with AR had significantly higher levels of eNO than healthy controls not depending on pollen season or pharmacotherapy. Increased eNO levels (p<0.001) were also found in patients with AR during the pollen season (21.25 ppb; IQR=20.3) compared to the levels outside the season (14.2 ppb; IQR=12.45) before treatment. In AR patients treated by nasal corticosteroids and antihistamines in the season were levels of eNO (18.6 ppb; IQR=14.63) significantly lower (p=0.044) than in the season before treatment (23.15 ppb; IQR=16.63). No difference was found in eNO levels in AR patients outside the season (14.2 ppb; IQR=13.38) and in the season after treatment (16.1 ppb; IQR=15.6).

**Conclusions:** This study has shown that patients with AR have significantly higher levels of eNO compared to healthy subjects and the levels of eNO increasing after pollen exposure. Application of topical corticosteroids and antihistamines caused significant decrease of eNO (almost to the starting levels) in the pollen season and pollen exposure. Application of topical corticosteroids and antihistamines should be considered for clinical decisions as changing current treatment.

**Reference:**


**P4033**

Variability of sputum inflammatory mediators in alpha-1-antitrypsin deficiency and usual COPD Helen Stone, Gillian McNab, Robert Stockley, Elizabeth Sapey. *ADAPT ProjectDepartment of Lung Function and Sleep, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; 2Cardiovascular and Respiratory Medicine, School of Medical and Dental Science, University of Birmingham, Birmingham, United Kingdom*

**Introduction:** There is inherent variability in the concentrations of inflammatory mediators in stable state sputum of usual COPD patients. Patients with alpha-1-antitrypsin deficiency (AAT) have a similar spectrum of lung disease and more inflammation but variability has not been assessed. Evidence for the efficacy of treatment in AAT is lacking; proof of concept (POC) studies indicate that augmentation increases AAT levels and reduces local mediator release. Our aims were to assess the daily variability of mediators in sputum in AAT, compared to usual COPD and to study the effects of sequential sampling to determine sample size for POC studies.

**Methods:** Interleukin 8 (IL8), myeloperoxidase (MPO) and leukotriene B4 (LTB4) were measured in the stable state spontaneous sputum of 12 patients with AAT and 12 usual COPD patients on 9 days over 1 month. The intra-patient variability was calculated (CV), compared between the groups, and the effects of combining results from multiple days for each patient were assessed.

**Results:** There was significant daily variability in all mediators, which was greater in usual COPD, despite ILS and LTB4 concentrations being higher (p<0.01) in AAT (medians 11.29 vs 3.72 mM; and 12.16 vs 6.10 mM respectively; 3 or 5-day rolling means) compared to both groups compared to a single days’ data (p<0.01) and reduced the number needed to show a 50% reduction in mediator as part of a POC study.

**Conclusion:** There is greater variability in usual COPD than AAT; though mediator levels were higher in AAT. Sequential sampling reduced intra-patient variability in both groups. Averaging 3 consecutive samples per patient was optimal.

**P4034**

The application of mass spectrometry to the analysis and characterization of protein and peptide composition in exhaled breath condensate of patients with pulmonary-endothelial disease Guzel Kireeva, Anna Ryabokon, Alykshey Kononikhin, Vladimir Bagdrov, Olga Pikon, Evgeniy Nikolaev. *1Department of Kinetics and Mechanisms of Enzymatic and Catalytic Reactions, Emanuel Institute of Biochemical Physics, Moscow; Russian Federation; 2Department of Ion and Molecule Physics, Institute for Energy Problems of Chemical Physics, Moscow, Russian Federation; 3Department of Oncological Biomarkers, Research Institute of Pulmonology, Moscow, Russian Federation; 4Department of Pulmonary Oncoology, Herzen Oncological Research Institute, Moscow, Russian Federation*

In recent years exhaled breath condensate (EBC) has been investigated more and more extensively as a matrix that reflects the composition of the airway-lining fluid and may contain biomarkers of diseases of respiratory system. The aim of this study is to compare identify proteins and peptides in EBC samples collected from two groups of people with healthy pulmonary system and with verified oncopulmonary diseases patients in the framework of the Scientific Research Oncology Institute with using mass spectrometry, as well as to compare proteome identification.

Proteins were collected using R-Tube, freeze dried, treated by trypsin and analyzed by nanoflow LC-MS/MS with a 7-Tesa Finnigan LTQ-FIT mass spectrometer (Thermo Electron, Germany), by means of Bioworks Browser 3.1 SR1 (Thermo Electron, Germany) were generated list of direct peptide mass and mass of their fragments, with following identification of proteins in the databases thought Mascot (Matrix Science version 2.0.04, the UK). At collected samples were identified peptides from more that 40 proteins of different nature, e.g. keratins and non-keratins. Peptides of nuclear ubiquituous casein and cyclin-dependent kinases substrate (NUCKS) which located in the nucleas in proliferating cells, glutamine synthetase (GS)-an enzyme that plays an essential role in the metabolism of nitrogen, alpha 1-antitrypsin (A1AT) is a protease inhibitor belonging to the serpin superfamily were discovered in disease EBC samples. They are uncharacteristic of healthy EBC samples. In conclusion, each of abnormal peptides, as well as their combinations, may have diagnostic value.

**P4035**

Circadian variation of exhaled breath temperature in healthy subjects Tanya Kralimarkova, Miroslava Rasheva, Tanya Grigorova, Zlatko Dimitrov, Dimitar Tihonirov, Roxana Mincheva, Vasil Dimitrov, Todor Popov. *Medical University Sofia, Clinic of Allergy and Asthma, Sofia, Bulgaria*

**Background:** Evaluation of the exhaled breath temperature (EBT) has been suggested as surrogate biomarker of airway inflammation, but there is no data on its circadian variation in health and disease. Measuring it by portable handheld device has been proven to be precise and highly reproducible. The aim of the study was to identify peaks and troughs in EBT around the clock in healthy individuals.

**Methods:** Forty two subjects (24 women; median age 26 years, age range 3 to 80 years) without history and objective signs of respiratory disease volunteered. EBT circadian influences need also to be considered as part of a POC study.

**Results:** EBT values showed a circadian pattern different from the one of A1AT - the acrophase (peak temperature) was registered at 19 h for EBT and at 13 h for A1AT. The bathyphase (trough temperature) was the same for both circadian rhythms at 1 h. Repeated measures analysis found both circadian fluctuations to be statistically significant (table):
P4036
Exercise test with dry air inhalation compared to mannitol test as marker of exercise induced asthma
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Objective: To compare exercise test with dry air inhalation and mannitol test to discriminate between different asthma treatments.

Methods: Exercise test with dry air inhalation (EIA test) (Aoolos bronchial challenge, Sweden) was compared to inhaled mannitol test in a randomized trial (NCT 00898933) on budesonide/formoterol (BF) as needed (n=23), budesonide (B; n=21) once daily, terbutaline (T) as needed (n=22) on exercise induced asthma (EIA) in mild asthmatic adults and adolescents. EIA test: 6 minutes treadmill run at 90% of max aerobic capacity; FEV1 measured before, and 0, 5, 10, 15, 30, 45 minutes after exercise. EIA test started with positive max fall in FEV1 ≥ 10% of baseline. Dry powder mannitol was inhaled in cumulative doses from 5 - 635 mg, to find the dose causing 15% FEV1 fall (PD15). EIA test was performed at trial start, after 3 and 6 weeks, mannitol test at trial start and after 6 weeks.

Results: Mean max FEV1 fall after EIA test was 16.34% at baseline and 13.11% after 6 weeks treatment. There was a significant improvement in BF (AFEV1 LS mean (95% CI) -5.4 (-8.93, -1.83) and B (-6.6 (+10.3, -2.96)) groups after 6 weeks, but not in the T group (+1.48 (-2.1, 5.59)). The mannitol test was positive (PD15=635 mg) in only 31/66 subjects at start, and in 22 at 6 weeks. All 66 subjects had a positive EIA test.

Conclusion: All patients had positive EIA test at baseline. The response to the EIA test improved significantly in two of the treatment groups (BF and T) and discriminated between the treatments. The mannitol test was positive in less than 50% of the subjects, and could not be used as outcome in the present study.

The study was sponsored by AstraZeneca.

P4037
Evolution of cellular inflammatory pattern in induced sputum in patients with mild-moderate asthma for five years
Elena Forenc, Elisabet Vera, Angela Fernandez, Jose Angel Carretero, Juan Antonio Domingo, Enrique Chacon, Salvador Bello. Pulmonaryology, Hospital Universitario Miguel Servet, Zaragoza, Spain

Background: Prospective study of cellular inflammatory pattern in samples of induced sputum can identify inflammatory changes in the natural history of asthma. The aim of our study is to know whether there are modifications of cellular inflammatory pattern in mild-moderate asthma along 5 years.

Materials and methods: The patients with mild- moderate asthma were studied along 5 years. The outcomes were: lung function FEV1 (% pred), no. exacerbations/year (EY), use of rescue therapy (RT), dose of inhaled corticosteroid/day (ICs), bacterial and viral cultures, total and differential cell count in induced sputum. Cellular inflammatory pattern was classified as eosinophilic (>2% of eosinophils), neutrophilic (>61% of neutrophils), paucigranulocytic (<1% of granulocytes). In 45% were found out differents patterns; 11% benign forms (2% of eosinophils), 11% inflammatory pattern in the sputum (11% eosinophilic, 11% neutrophilic y 33% supernatant in smoking asthma). In 45% were found out differents patterns; 11% benign forms (2% of eosinophils), 11% inflammatory pattern in the sputum (11% eosinophilic, 11% neutrophilic y 33% supernatant in smoking asthma).

Results: The study began with 24 patients and in 18 we repeated the induced sputum 5 years after. The probability were of 100%. 55% showed the same cellular inflammatory pattern in the sputum (11% eosinophilic, 11% neutrophilic y 33% paucigranulocytic). In 45% were found out differents patterns; 11% benign forms (2% of eosinophils), 22%agressive forms (neutrophilic, eosinophilic o mixed) and a 11% changed the inflammatory pattern but with agressive forms too.

Conclusions: In stable patients with mild-moderate asthma, the most recurrent inflammatory pattern is thepaucigranulocytic. The positivity of bacterial cultures in sputum may be the cause of the changes in the induced sputum to agressive forms. Nonsignificant changes towards neutrophilic patterns have been observed that warrant further study in larger groups.

P4038
Safety and efficacy of inhaled mannitol as a bronchial provocation test in asthmatic children
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Background: Bronchial provocation with inhaled mannitol is a new and simple test for osmotic bronchial challenge. The aim of this study was to determine the efficacy and safety of inhaled mannitol in asthmatic children.

Methods: Sixty five children (54% males) aged 6-12 years, with established diagnosis of Childhood, were studied. An asthma control questionnaire (CACT) was completed before bronchial provocation. A commercial preparation of dry powder mannitol was administered in progressively increasing doses according to the standard protocol, and the FEV1 was measured 60 seconds after each dose. The procedure ceased when a 15% fall in FEV1 was achieved (positive challenge) or the cumulative dose of 635 mg was reached (negative challenge). In case of a positive provocation, the dose of mannitol (mg) to provoke a 15% fall in FEV1 (PD15) was calculated. Adverse events during and 2 hours after the test were also documented.

Results: Twenty four children (36.9%) were positive to the mannitol challenge, with a maximum mean±SE FEV1 fall of 18.7±4.1%, and a median PD15 of 125 mg (range 18- to 470 mg). There was a significant correlation between PD15 and C-ACCT score (r = 0.58, p<0.001). The most common adverse events were: cough (83.1% - 100% in those with a positive challenge), nausea (9.2%), headache (4.6%), and abdominal pain (1.5%). No adverse effect was present at 2 hours after test.

Conclusion: Bronchial challenge with mannitol is safe and correlates well with the level of asthma control in asthmatic children.

P4039
Comparison of two devices and two breathing patterns for exhaled breath condensate sampling
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Background: Analysis of exhaled breath condensate (EBC) provides a non-invasive access to the lung epithelial lining fluid.

 Aim: Comparison of two commercially available portable devices (RTube, ECo- Screen turbo), and evaluation of different breathing patterns with regard to marker proteins and the source of EBC in healthy adults.

Methods: EBC was collected from 10 subjects 4 times in a cross-over design, for each device once during tidal breathing and once hyperventilating. Conductivity, pH, PHA surfactant protein A (SPA), Clara-cell protein (CCP) and total protein in EBC were assessed. Data on the volatile organic compound (VOC) profile of the EBC were obtained using the electronic nose Cyanose 320TM.

Results: RTube provided a higher sample volume compared to the ECoScreen. Hyperventilation yielded higher volumes than tidal breathing. Neither devices nor breathing patterns affected pH. Although conductivity appeared to be affected by both, average measurements remained rather stable. Hyperventilation led to an increase of total protein. The ECoScreen showed a trend towards higher protein amounts. CCP and SPA amounts were not influenced by the breathing pattern. The electronic nose was capable of distinguishing between breathing patterns and devices.

Conclusion: EBC pH and to a lesser extent conductivity are fairly stable measures that do not depend on device or breathing pattern. Hyperventilation increases total protein concentration possibly via augmented shear forces and increased aerosol production, but not through increased alveolar ventilation, as SP-A amounts were not altered by hyperventilation. The VOC content of EBC seems to be influenced by device and breathing pattern.

P4040
Prostaglandin E2 and cysteinyl leukotriene concentrations in sputum supernatant in smoking asthma
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Background: Smoking may modify airway inflammatory pattern. There is some evidence that the elevated levels of PGE2 in the exhaled breath condensate of patients with asthma are mainly related to smoking habit [Kostikas et al ERJ 2003].

Objective: To evaluate the concentrations of PGE2 and cysteinyl leukotrienes in sputum supernatant in patients with asthma and to determine whether smoking affects significantly their measurements.

Methods: We studied 98 patients with asthma (47 smokers), under optimal treatment with ICS. We also studied 40 control subjects (20 smokers). All subjects underwent sputum induction, pulmonary function tests, measurement of FeNO and BHR to methacholine expressed as PD15. We also studied 40 control subjects (20 smokers). All subjects underwent sputum induction, pulmonary function tests, measurement of FeNO and BHR to methacholine expressed as PD15.

Results: Median [IQR] sputum cysLTs concentration was significantly higher in smokers compared to non-smokers [121 (95,175) pg/ml, respectively; p<0.001]. The most common adverse events were: cough (83.1% - 100% in those with a positive challenge), nausea (9.2%), headache (4.6%), and abdominal pain (1.5%). No adverse effect was present at 2 hours after test.

Conclusion: Bronchial challenge with mannitol is safe and correlates well with the level of asthma control in asthmatic children.

737s
**P4041**

Adaptation of differential ion mobility spectrometry (DMS) for discrimination of specific biomarkers in exhaled breath in patients with severe renal-pulmonary dysfunction

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Introduction: Volatile substances (VOC’s) in exhaled breath are target for identification of new biomarkers for disease and metabolic processes. Renal insufficiency could be a good example of an illness with exhaled markers of an internal disease.

The ion mobility spectrometry (IMS) is a method for detection of volatile compounds in exhaled air with a sensitivity in ppt-range. The method was used in a pilot study for discrimination of patients with chronic metabolic kidney disease.

Methods: A DMS of STIONEX was used for analysis of exhaled breath. The measurements were performed before and after a dialysis procedure. The DMS-analysis includes a pre separation by a multi-capillary tube, ionization of the sample and measurement of ions by IMS with 270 sec. Spectra were discriminated by detection of clusters and calculation of significance using support vector machine.

Results: It was possible to collect sufficient samples in all patients. Specific clusters of biomarkers were found discriminating marker exhalation before and after therapeutic intervention with dialysis. Specific clusters, indicating drug-uptake, were found.

The inter-individual reproducibility was very high, which possibly represents the manifold drug-treatment and severity of renal insufficiency with enhanced blood urea.

Discussion: Characteristic breath pattern could be detected. The method is non-invasive and fast and could offer new possibilities for long term control of medicaments and chronic metabolic disorders. Further studies are needed to identify certain markers and metabolites.

**P4042**

Clusters of biomarkers in exhaled breath detected by differential ion mobility spectrometry (DMS)

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Introduction: Non invasive biomarkers from exhaled breath became high interest. The ion mobility spectrometry has better sensitivity and differentiation of volatile compounds than their gas-chromatography. The high sensitivity of the method brings a couple of problems due to VOC’s from ambient air and environment.

Methods: The aim of the study was to demonstrate standardized sampling, reproducibility and the discrimination of groups of volunteers by exhaled markers. The calculation of spectra and statistical discrimination was performed using a statistic program based on a Support-Vector Machine.

For the investigation were included 57 volunteers, whose were recruited from two completely different environmental-occupational ambient air conditions.

Results: There were collected repetitive samples on one day and within one week for each. Similar tests were performed on ambient air.

It was possible to demonstrate significant differences in spectra of volunteers. It was possible to differentiate clusters from human biomarkers from the clusters which represent VOC’s from ambient air. Subgroups, e.g. sex, BMI, smoking, were possible to discriminate without disturbance from ambient conditions.

Discussion: The DMS is suitable for the detection of VOC’s in exhaled breath even in different environmental conditions. The fingerprints (clusters) in each measurement are characteristic for the individuals, groups and highly reproducible. Specific VOC’s from ambient are can be mostly excluded from patients markers. The ion mobility spectrometry may be a sufficient method for non-invasive detection of disease markers in breath.

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of moderate bronchial asthma (BA). The control group consisted of 58 healthy volunteers. The EBC was collected in all patients, as well as the TNF concentration in EBC was measured before and after the course of therapy by spectrophotometric method expressed as TTN. The TNF was measured in patients with BA than in control.

**Conclusion:** The measurement of TNF concentration in EBC can be used as a marker of airway inflammation in patients with moderate BA for the monitoring of patient’s status. During the course of therapy the statistically significant decrease of this parameter was demonstrated; that is strongly correlated with clinical status. So, the TNF level in EBC also can be considered as a sensitive marker of the efficacy of the therapy administered.

### P4046

**Increased levels of osteopontin in sputum supernatant in smoking asthma**

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**Background:** Osteopontin (OPN) has been associated with inflammation and fibrosis. OPN is increased in asthma and is related to the underlying severity and to factors expressing to baseline and inflammation. Smoking may modify the inflammatory pattern of the airways.

**Aims and objectives:** To evaluate the levels of OPN in sputum supernatants of asthma patients and to investigate the possible role of smoking as well as associations with mediators and cells involved in the inflammatory and remodeling process.

**Methods:** We studied 98 asthma patients (51 smokers) and 40 healthy subjects (20 smokers). We undertook lung function tests, bronchial hyperresponsiveness to methacholine, and sputum induction for cell count identification and measurement of OPN, VEGF, TGF-β1, CysLTs, IL-13, ECP and IL-8 in supernatants. The concentrations of all mediators were measured using enzyme immunoassays.

**Results:** Median OPN levels (pg/ml) were significantly higher in smoking asthma (SA) compared to non-smoking asthmatics (NSA), and both smoking and non smoking controls [120 (651, 1793) vs 210 (120, 404) vs 50 (42, 70) vs 102 (71, 156) pg/ml, respectively; p < 0.0001]. Regression analysis provided significant associations between log OPN and sputum neutrophils, IL-8, IL-13 and TGF-β1. The most significant association of TGF-β1 was the one with OPN. These associations were observed only in SA. No significant associations were observed between OPN, lung function tests and PD15 to methacholine in all groups.

**Conclusions:** OPN levels are affected by the smoking habit in asthma. The associations of OPN with sputum neutrophils, TGF-β1, IL-13 and IL-8, only in SA, suggest a possible role for OPN in the inflammatory and remodeling process in SA.

### P4047

**Laboratory investigation of sputum and mucociliary clearance (MCC) condition in patients with COPD**

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**Aim:** To investigate biochemical parameters of sputum for evaluation of MCC’s disorders in patients with COPD.

**Materials:** 90 smoking patients with COPD in stable condition.

**Methods:** Biochemical parameters of sputum (medium weight molecules (MWM), trypsin, cysteine proteases cathepsin B, cathepsin L, α1-proteinase inhibitor (α1-PI)) were measured with ELISA. EBC was collected during 10 minutes of tidal breathing. IL1β, IL6, IL8 and TNFα were measured with ELISA.

**Results:** The concentration of inflammatory cytokines in exhaled breath condensate (EBC) in children with IBD were studied during 10 minutes of tidal breathing. IL1β, IL6, IL8 and TNFα were measured with ELISA.

**Conclusions:** The elevated concentration of inflammatory cytokines in EBC in children with IBD can suggest that inflammation, which plays the key role in pathogenesis of IBD, may be also present in respiratory tracts.

### P4049

**Effects of outdoor temperature and humidity on methacholine challenge tests**

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This study tried to evaluate whether outdoor daily temperature (T) and humidity (H) influence methacholine test results in outpatients living in temperate climate areas. 4.232 subjects (2391 males; age 35.1 ± 16.15; FEV1, 100.36% [IQR: 92.34-108.81]) that performed a methacholine test for a suspected bronchial asthma between 2000 and 2010 were considered. Mean outdoor temperatures (°C) and relative humidity (%) were measured at the time of the test. Patients with bronchial hyperresponsiveness (PD20 < 1.28) were used as controls (n = 2329). Patients with bronchial hyperresponsiveness (PD20 < 1000 pg/ml) were used as controls (n = 2329). This study showed that an increase in temperature (excluding extreme values) is associated to a slight, but significant, reduction of bronchial hyperresponsiveness risk.

### P4050

**Are FENO indices useful diagnostic tools in suspected asthma? Experience of a routine lung function laboratory**

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**Background:** Asthma diagnosis is based on symptoms associated with airflow obstruction and decreased bronchodilator responses. FENO is a non-invasive, reproducible method to detect inflammation in the airways. FENO is defined as the concentration of NO in exhaled breath condensate (EBC) when a known volume of air is exhaled into a closed system.

**Aim of the study:** To evaluate the concentration of inflammatory cytokines in exhaled breath condensate (EBC) in children with IBD. The aim of the study was to evaluate the concentration of inflammatory cytokines in exhaled breath condensate (EBC) in children with IBD.

**Method:** FENO indices were collected from 24 children with IBD (12 boys and 12 girls, mean age 13.8 ± 3.3) and 37 healthy volunteers (20 boys, 17 girls, mean age 13.9 ± 3.6) were enrolled into this study.

**Results:** FENO values were significant lower in children with IBD compared to healthy volunteers (p < 0.05). The causes of asthma in the children could be considered as a diagnostic tool for the early detection of asthma in children with IBD. This study showed that an increase in temperature (excluding extreme values) is associated to a slight, but significant, reduction of bronchial hyperresponsiveness risk.
variability. Airway inflammatory component measured by exhaled nitric oxide (FENO50) has been proposed as a diagnostic tool but remains controversial.

**Aims:** To assess the ability of FENO indices to identify bronchial hyperresponsiveness to methacholine (PC20M < 16mg/ml) and to establish which respiratory symptoms relate to FENO indices and PC20M.

**Methods:** We conducted a prospective study on 174 steroid naïve patients addressed for PC20M. Patients with respiratory symptoms, FEV1 ≥70% pred and no proof of reversibility to inhaled salbutamol (either not done or response <12%) completed a questionnaire about their symptoms and underwent FENO measurements at different flow rates (50-100-150 and 200ml/sec) and PC20M.

**Results:** 82 had a PC20M <16mg/ml and had significantly higher FENO50, FawNO and Intercept but did not show significant difference in CAV(NO) value. By constructing ROC curve, we found that FENO50 cut-off value of 34 ppb is able to identify bronchial hyperresponsiveness with high specificity (95%) and PPV (88%) but low sensitivity (35%) and NPV (62%). For the whole group, the dose-response slope (DRS) for methacholine weakly correlated with FENO50 but not with CAV(NO). Among the positive PC20M, there was no relationship between the magnitude of PC20M and the level of FENO indices. Wheezing was the symptom most convincingly associated with raised FENO50.

**Conclusion:** FENO50 ≤34ppb is a good diagnostic criterion in patients with suspected asthma. However FENO50 ≤34ppb clearly does not rule out bronchial hyperresponsiveness and should prompt the clinician for asking methacholine challenge.

### 418. Treatment strategies, systemic manifestations and biomarkers in airway diseases

**P4052**

**Markers of airway inflammation and airway hyperresponsiveness remain stable in untreated asthmatics over time**

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**Introduction:** Airway hyperresponsiveness (AHR) and airway inflammation are important hallmarks of asthma that may be used in asthma monitoring, but may also vary between asthmatics as a potential indication of different clinical asthma phenotypes. The aim of our study was to assess whether two commonly used measures, AHR to mannitol and exhaled NO (eNO), were stable over a period of time in asthma patients who were not treated with steroids.

**Materials and methods:** A total of 54 non-smoking, asthmatics not treated with steroids were enrolled in the study and assessed at baseline and again three to six months later, where spirometry, skin prick test and induced sputum was performed as well as measurements of hyperresponsiveness to mannitol and eNO. Subjects were excluded if they experienced a worsening of their asthma or commenced on steroid treatment.

**Results:** A total of 41 subjects (21 females, mean age: 41 years, 70.70% atopic) completed both visits. Mean PEVi% predicted at baseline was 94.13% (SD 17.71). There was a significant correlation between the degree of AHR, defined as well as measurements of hyperresponsiveness to mannitol and eNO. Subjects were excluded if they experienced a worsening of their asthma or commenced on steroid treatment.

**Conclusion:** In asthmatics not treated with steroids, markers of AHR and airway inflammation remain at the same level over a three to six months period of observation, suggesting that these are stable markers of clinical disease.

**P4053**

**Airway resistance and reactance in COPD patients and healthy smokers, and effect of bronchodilators**

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**Background:** Little is known about the reversibility response of the obstructive pattern to therapies in COPD. Impulse oscillometry (IOS) is a method to measure resistance and reactance of both the central and peripheral airways.

**Aim:** The aim of this study was to investigate how salbutamol and ipratropium, commonly used in COPD, affect obstructive airway patterns measured by impulse oscillometry.

**Methods:** Twenty two healthy smokers and 24 patients with COPD, with matched pack years were included in this study. Spirometry and impulse oscillometry were performed at baseline, after inhalation of salbutamol and after additional ipratropium.

**Results:** Medication increased PEVi1 as expected. COPD patients had significantly higher total (R5), central (R20) and peripheral (R5-R20) resistance (% predicted) at baseline compared to healthy smokers. After medication with salbutamol, R20 decreased in both COPD patients and healthy smokers. Salbutamol only decreased R5-R20 in COPD patient, but after additional ipratropium the R5-R20 in healthy smokers also decreased. The COPD group showed a higher reactance (X5, AX and FRES) at baseline compared to the healthy smokers. After inhalation of salbutamol, X5, AX and FRES was significantly decreased in the COPD group as well as in healthy smokers. Additional inhalation of ipratropium showed a tendency of decreasing X5 and AX in both COPD patients and healthy smokers.

**Conclusions:** COPD patient have higher resistance and reactance compared to healthy smokers at baseline. Both airway resistance and reactance was affected by inhalation of salbutamol and additional ipratropium, and more pronounced in COPD patients compared to healthy smokers.

**P4054**

**Monitoring of efficacy of therapy with monoclonal antibodies – Omalizumab = Using the Recovery-ELISA**

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The Reversibility-ELISA (R-ELISA) resembles a combination of a Sandwich-ELISA for the antigen and a competitive ELISA for the therapeutic antibody. The R-ELISA is a special ELISA application for presence of an additional TAB in the measuring system. The special feature is a two-dimensional calibration, which performs a calibration for the antigen without and with addition of the therapeutic antibody and a calibration of the antigen-recovery in dependence of the therapeutic antibody.

Addition of Omalizumab to the IgE-Sandwich-ELISA reduced the optical density of the signal in a non-linear manner for the detection of IgE. At 7.2 μg/ml Omalizumab the IgE-signal is reduced by 75%. The addition of substrate to the assay enables the re-calculation for real samples. The Fig. shows the antigen recovery in dependence of Therapeutic antibody.

**P4055**

**Predicting performance of cough reflex sensitivity, exhaled nitric oxide (eNO) and bronchial responsiveness for efficacy of bronchodilator therapy on isolated chronic non-productive cough**

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**Background:** Chronic cough responding to bronchodilator therapy (BDT) was originally reported as cough variant asthma (CVA), in which bronchial responsiveness was shown to be mildly increased. Our aim was to elucidate whether cough reflex sensitivity, exhaled nitric oxide (eNO) and bronchial responsiveness could predict efficacy of BDT on chronic non-productive cough.

**Methods:** Consecutive patients with non-productive cough lasting at least 8 weeks who visited our respiratory medicine clinic from 2005 to 2010 and gave informed consent for participating in this study were enrolled. Exhaled NO, capsaicin cough sensitivity (CS) and bronchial reversibility were measured in this order at their first visit. Bronchial responsiveness (PC20) was measured at their second visit following 6-day BDT.

**Results:** The study protocol was fully completed in 117 patients. Multivariate regression analysis revealed that only CS was significantly (r=0.430, p<0.0001) correlated with the VAS scale. The ROC curve showed that the optimal cut-off
value of C5 to predict MI on the efficacy of BDT on cough was solution number of 4.5 (2.8 mmol/L) with a sensitivity of 0.81 and specificity of 0.72.

The observed comorbidities in COPD is closely related to systemic inflammation however we think that the exact mechanism of each comorbidity needs to be further investigated.

**P4058**

Is the body mass index a determinant of inflammatory status and quality of life in asthma?

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**Introduction:** The aim of our study was to determine the relationship between body mass index (BMI), alveolar nitric oxide (CaNO), and the health status of asthmatics by applying the quality of life questionnaire Sydney-modified (AQLQ-S).

**Material and methods:** We studied 139 asthmatics (GINA) between 15 and 75 yr of age (men 45 and women 94) and several degrees of severity. We measured anthropometric variables, baseline spirometry, and nitric oxide exhaled (eNO) at multiple flows (50, 100, 150, 200, and 250 ml/s). Bronchial nitric oxide (BDT) and CaNO were assessed according to Tsoukas model. All patients completed the AQLQ-S questionnaire. For comparisons between two groups, T-test student was used. The relations between NO parameters and other markers were analyzed with partial correlations adjusted for asthma severity.

**Results:** The mean BMI was 26.46±4.97 kg/m², CaNO 3.89±4.7 ppb and JaoNO 2.41±3.270 m/s. There were no statistically significant differences in values of CaNO and JaoNO between obese asthmatic group and non obese. The AQLQ-S scores obtained were (mean ± SD): total score: 5.62±1.08; shortness of breath: 5.73±1.14; mood: 5.21±1.24, social restriction: 5.92±1.25, and concern: 5.69±1.10.

**Correlations between BMI and AQLQ-S scores**

<table>
<thead>
<tr>
<th>Correlation between</th>
<th>BMI</th>
<th>Sig (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMMI</td>
<td>0.870</td>
<td>0.000</td>
</tr>
<tr>
<td>Active form of FcRII after ILF stimulation</td>
<td>0.422</td>
<td>0.012</td>
</tr>
<tr>
<td>CD11b after ILF stimulation</td>
<td>0.415</td>
<td>0.013</td>
</tr>
<tr>
<td>CCR3</td>
<td>-0.402</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Conclusion:** A low BMI is associated with a low grade systemic inflammation in COPD patients visualized by systemic activation of neutrophils. In COPD patients the FFMI correlated with BMI, which suggests that the systemic inflammation in COPD patients is associated with a muscle wasting phenotype.
P4060
Analysis of atherosclerosis in patients with chronic obstructive pulmonary disease by carotid ultrasonography
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Rationale: Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of cardiovascular events. Atherosclerosis is an independent predictor of cardiovascular disease. We tested the hypothesis that there is a close association between atherosclerosis and disease severity of COPD.

Methods: We recruited 46 subjects with COPD (45 male-1 female, 42 ex-smokers, 4 current smokers, aged 74.7 ± 7.9 years). All subjects underwent speimetry and carotid ultrasonography. The severity of COPD was determined by GOLD Staging System for COPD Severity Definition. We measured carotid intima-media thickness, and determined the maximal intima-media thickness (IMTmax) value as the indicator of atherosclerosis.

Results: Average IMTmax value in all subjects was 1.9 ± 1.1 mm. IMTmax value was 2.2 ± 1.2 mm in stage I (n=3), 1.7 ± 1.0 mm in stage II (n=15), 2.0 ± 1.1 mm in stage III (n=16), and 2.0 ± 1.4 mm in stage IV (n=12). There were no differences of IMTmax values among the stages of COPD. IMTmax values were higher in subjects with ischemic heart disease (n=5) compared to those without ischemic heart disease (n=41) (IMTmax value: 2.7 ± 1.6 mm vs. 1.9 ± 1.1 mm, p < 0.05). 3 subjects had lower intima-arteries obstructions (IMTmax value was 2.1 ± 0.7 mm).

Conclusions: Atherosclerosis was not associated with disease severity of COPD. This study suggests that atherosclerosis progresses even in patients with mild COPD, especially in those who are associated with ischemic heart disease.

P4061
Body composition analysis on COPD patients – Results of prospective study
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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is in close relation to chronic systemic inflammation involving an extrapulmonary pathology. The results can be weight and muscle loss and nutritional abnormalities. FFMI (Fat Free Mass Index) is an important measure in COPD patients to determine the progression of the muscle affection.

Aims: To determine FFMI and BMI in COPD patients (pts).

Methods: In 2010, we began BC analysis on COPD patients with Dual-Energy X-ray Absorptiometry (DEXA) in a prospective study trial. We analysed BC of 30 clinically stable COPD pts in stage II-IV GOLD. There were 24 M, median age 69 yrs (49-84 yrs) and 6 F, median age 74 yrs (51-85 yrs). For body composition analysis by DEXA we used Hologic Discovery Wi including the software “Whole Body Composition Analysis”. Reference intervals (by Schutz) for FFMI were used.

Results: In M median BMI was 23 (17.7-33.9) and 23.34 (14.79-37.49) in F respectively. FFMI was 17.78 (14.52-22.18) and 15.47 (12.41-20.36) respectively. 13/30 pts had FFMI under the 10th percentile for their gender and age category, 16/30 pts had FFMI under the 25th percentile. The highest prevalence of low FFMI was seen in GOLD stage IV.

Conclusions: In our group, most of pts had FFMI <25th percentile. Those pts with FFMI<10th percentile have a higher risk for future physical disability. In our opinion, pts with FFMI <25th percentile need help to change their dietary habits, physical rehabilitation and nutrition support to prevent the progression of disease. Determination of FFMI would help to create procudulas formulas for COPD pts with muscle weakness and/or terminal cachexia.

P4062
Identification of microorganisms based on gas chromatography-mass spectrometry analysis of volatile organic compounds in headspace gases
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Results: Average IMTmax value in all subjects was 1.9 ± 1.1 mm. IMTmax value was 2.2 ± 1.2 mm in stage I (n=3), 1.7 ± 1.0 mm in stage II (n=15), 2.0 ± 1.1 mm in stage III (n=16), and 2.0 ± 1.4 mm in stage IV (n=12). There were no differences of IMTmax values among the stages of COPD. IMTmax values were higher in subjects with ischemic heart disease (n=5) compared to those without ischemic heart disease (n=41) (IMTmax value: 2.7 ± 1.6 mm vs. 1.9 ± 1.1 mm, p < 0.05). 3 subjects had lower intima-arteries obstructions (IMTmax value was 2.1 ± 0.7 mm).

Conclusions: Atherosclerosis was not associated with disease severity of COPD. This study suggests that atherosclerosis progresses even in patients with mild COPD, especially in those who are associated with ischemic heart disease.

P4063
Pathological changes in the skeletal muscles in COPD patients
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Background: Peripheral muscle weakness is a major problem in COPD, compromising the ability to exercise intolerance and decreased health status. The loss of muscle mass has been described in those patients, but little data are reported regarding the morphology of limb muscles.

Objectives: To study the pathological changes that occurs in the peripheral skeletal muscles in COPD Patients.

Methods: 50 COPD patients were chosen from the outpatient clinic of chest dis- eases, Cairo University Hospitals. Muscle biopsies were taken from the left Vastus lateralis under local anesthesia by Abram’s needle and subjected to histopatho- logical examination after staining with Hematoxylin and Eosin. The biopsies were compared to specimens taken from 10 healthy control subjects of the same sex and age group.

Results: Strong correlation was found between the severity of COPD and the degree of muscle atrophy graded from zero (normal) to 4 (marked atrophy) according to number of foci of atrophy. The one patient in stage I & 69% of patients in stage II COPD were found to have normal biopsy. Stage III, showed both mild atrophy in (45.5%) & moderate atrophy in (41%) of patients. Stage IV showed moderate atrophy in (64.3%). Marked degree of atrophy were belonged to stage III-IV & IV. 7.2% of patients. A statistically significant positive correlation was found between degree of muscle atrophy and (age, smoking index & number of exacerbations/year).

Conclusion: COPD patients showed variable degrees of peripheral skeletal muscle atrophy correlated to disease severity. Progression of COPD is associated with progression of the muscle affection.

P4064
Plasma VEGF correlates with right ventricular function in pulmonary hypertension
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Introduction: Pulmonary hypertension (PH) is a severe, progressive condition of the small pulmonary vessels that leads to increased pulmonary vascular resistance, right ventricular failure and death. Previous studies suggest the role of VEGF (vascular endothelial growth factor) in the pathomechanism of PH by several path- ways. Still, the relationship between airway VEGF and right ventricular function has not been investigated yet.

Aims: We aimed to evaluate the exhaled breath condensate (EBC), as an airway sampling technique for VEGF detection in subjects with PH and to compare EBC and plasma VEGF with the best noninvasive clinical sign of advanced disease, by measuring right ventricular longitudinal function, tricuspid annular plane systolic excursion (TAPSE).

Methods: 10 PH patients (6 IPAH, 2 CTEPH, 1 scleroderma, 1 congenital heart disease, 58.17 years, mean pulmonary pressure 58.21 mmHg), and 9 healthy controls (50±13 year) participated in the study. Plasma and EBC (Ruthe, Charlotteswile, US) were collected for VEGF measurements (Quantikine ELISA kit, R&D) and echocardiography was performed to assess TAPSE.

Results: In EBC the VEGF concentration was under the limit of detection in both groups. The level of plasma VEGF was significantly higher in the patient group than in controls (130.49 pg/ml; 30.40 pg/ml; p=0.004). We found significant correlation between TAPSE and plasma VEGF level in PH patients (p=0.02, r=0.69).

Conclusion: We suggest, that decrease of VEGF with advanced PAH disease can be a result of deterioration of right ventricular contractility accompanied with...
Comorbidities in the course of chronic obstructive pulmonary disease
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Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and frequent co-morbid conditions.

Purpose: To evaluate the prevalence of comorbidities in patients with COPD and assess correlations between Body Mass Index (BMI) and exacerbations.

Methods: Retrospective study including 120 patients with COPD. Symptoms, spirometry, peripheral oxygen saturation, BMI and comorbidities were obtained from patient records.

Results: The mean age was 63.3±23 years. All patients were smoking for more than 10 years. 65.8% of patients had comorbidities and the most frequent ones were: systemic hypertension (52.5%), diabetes (32.5%), heart failure (20.8%), renal failure (8.3%), anemia (8.3%), lung cancer (7.5%) and sleep apnea syndrome (SAS) (3.3%). Mean rate of exacerbations was 1.6±0.4. Patients with comorbidities had more exacerbations (2.4±0.4) than those without comorbidities (0.8±0.3).

Conclusions: Comorbidities are very common in COPD. They are associated with more severe exacerbations. Results indicate a relation between BMI and rate of exacerbations.

Usefulness of a panel of sputum markers in the evaluation of lung inflammation and functional impairment in symptomatic smokers and COPD patients
Guglielmo Guglielmi1, Stefano Calzetta2, Riccardo Tagliabue3, Monica Capogrossi1, Maria Chiara Calzetta4, Annarita Vestri4, Giovanni Puglisi5, Fulvio Benassi6, Ilio Cammarella7, Antonio Santini8, Matteo Magi9, Claudio Terzano2.

Background: COPD is a major cause of morbidity and mortality worldwide. COPD patients have a greater number of exacerbations requiring hospitalization or emergency room visits with increased healthcare costs. Comorbidities are common in COPD patients and may alter the natural course of the disease. Sputum analysis may provide useful information about the airway inflammation of COPD patients. The aim of the study was to evaluate the usefulness of a panel of markers identified in the literature that may be useful in the assessment of airway inflammation in COPD patients.

Methods: We enrolled 60 patients with COPD (30 with COPD and 30 without COPD). All patients underwent a physical examination and spirometry. Blood and sputum samples were collected and analyzed for a panel of markers including neopterin, IL-8, MMP-9, HNP, HNE, and IL-18.

Results: A significant correlation was found between the sputum markers and the clinical characteristics of the patients. The markers were found to be different between the two groups of patients with and without COPD. The markers that showed the greatest differences were neopterin, IL-8, and MMP-9. The markers that showed the least differences were HNP and HNE.

Conclusions: The panel of markers identified in this study may be useful in the assessment of airway inflammation in COPD patients. Further studies are needed to validate the potential utility of these markers in the management of COPD patients.

Airway and inflammatory profile of ORL rats: An asthma phenotype?
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Introduction: The ORL rat is a Long Evans strain with inherited cryptorchidism. We have observed respiratory distress and wheezing in a subset of this strain but no respiratory phenotype is available.

Objective: We hypothesized that ORL rats would exhibit airway responsiveness (AR) associated with inflammation. To address this question, we investigated...
whether respiratory mechanics and biomarkers of inflammation in these rats would be different at baseline (BL) or during methacholine (MCh) challenge induced congestion.

Material and methods: Long Evans WT (n=9) and OXL (n=14) rats were anesthetized, tracheostomized, placed in a plethysmograph (Buxco, Rodent RC Site), mechanically ventilated and challenged with 0.3 to 12.5 mg/ml of aerosolized MCh. We calculated resistance (R) and compliance (C), and lung tissue homogenates were assayed for IL-4, IL-6, and TNF-α using ELISA. Quantitative histomorphometry is ongoing. We performed 2-way ANOVA of physiological outcomes and inflammatory markers.

Results: Respiratory challenges with MCh increased R and decreased C as a function of dose and group (WT vs. OXL). OXL rats had increased (p < 0.0001) sensitivity to MCh for R. IL-6 and IL-4 expression was decreased by 23% (p < 0.0001) and 77% (p < 0.0001), respectively in OXL rats with no differences in TNF-α as compared to WT rats.

Conclusions: OXL rats compared with WT rats were significantly more responsive to MCh challenges, indicated large and small airway reactivity and exhibited decreased expression of IL-6 and IL-4 in lung tissue. The observed respiratory reactivity in this strain of OXL rats may provide a genetic animal model for the study of asthma and associated genetic/hormonal/environmental factors.

449. Diagnosis and treatment of inflammatory respiratory diseases

P4070 Impact of pulmonary tuberculosis infection on chronic obstructive pulmonary disease
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Background: Tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) are common diseases in developing world, sharing some risk factors like smoking and low socioeconomic status.

Aim: To find out whether TB is a risk factor of COPD and to investigate any changes in COPD patients having TB infection compared to non TB cases.

Method: Retrospective study of 328 pulmonary function test (PFT) diagnosed COPD cases was done. Data of 81 patients with clinical and radiological signs of COPD, multiple bullae on radiography without lung function measurements were also taken. Control cases are 414 patients who had done chest radiography from different departments besides respiratory unit.

Result: 328 PFT diagnosed COPD patients, 141 had radiological feature of TB but only 32 of 414 control cases had those features. Odds ratio (OR) was 9.001 compared to placebo) in 10 out of the 15 patients (66.7%) (p < 0.001 compared to both control groups). All asthmatic responses were initiated with a mean 8-hour latency, were recorded at more than three consecutive time points and were sustained until the end of the 12-hour time period.

Conclusions: Specific nasal challenge could be a reliable and specific tool for the diagnosis of Alternaria-induced asthma, alternatively to bronchial challenge, in case confirmation of mould implication is necessary.

Results: Specific nasal challenge in the diagnosis of alternaria-induced asthma
Dimitrios Latisios, Despoina Papakosta, Konstantinos Peropodi, Theodoros Kontsikas, Chloé Ayratou, Katerina Manika, Dimitrios Gionelekas, Konstantinos Zarogoulidis. Pulmonary Department, Aristotle University of Thessaloniki, G. Papamakousa Hospital, Thessaloniki, Greece

Background: Allergic sensitization to Alternaria has been identified as a risk factor for the development and persistence of asthma and is associated with severe and life-threatening episodes. The interaction between upper and lower airways has not been investigated for Alternaria.

Aims and objectives: To investigate whether specific nasal challenge with Alternaria allergen can be used as a diagnostic tool for Alternaria-induced asthma.

Patients and methods: The study included 15 adults patients with mild asthma sensitive to Alternaria and two control groups: 1) 8 patients with mild, allergic asthma non-attributed to Alternaria and 2) healthy controls. Diagnosis of asthma was already established by positive both reversibility and methacholine test. Two nasal provocation tests were performed, one with normal saline (placebo) and another with Alternaria antigen (specific nasal challenge, SNC) performed at two different days, FEV1 was measured during a 12-hour period, at 18 time points and another with Alternaria antigen (specific nasal challenge, SNC) performed at two different days, FEV1 was measured during a 12-hour period, at 18 time points.

Results: A significant FEV1 decline > 20% from baseline (26.9±2.3%) was recorded after SNC (p<0.001 compared to placebo) in 10 out of the 15 patients (66.7%) (p<0.001 compared to both control groups). All asthmatic responses were initiated with a mean 8-hour latency, were recorded at more than three consecutive time points and were sustained until the end of the 12-hour time period.

Conclusions: Specific nasal challenge could be a reliable and specific tool for the diagnosis of Alternaria-induced asthma, alternatively to bronchial challenge, in case confirmation of mould implication is necessary.
P4074
Mild asthmatic patients consistently respond to natural, low dose, allergen challenge in EEC
Deepen Patel1, Navyen Patel1, Joanne Lee2, Peter Cournou3, Rod Hafner1, Anne Marie Salapatek2
1Medical Affairs, Cetene Research, Mississauga, Canada; 2Research & Development, Cetene Research, Mississauga, Canada; 3Research & Development, Circausis Ltd., Oxford, United Kingdom

Introduction: The cat allergen, Felis domesticus (Fel d1), is a common trigger of allergic rhinoconjunctivitis and asthma exacerbation. Aerosolized Fel d1 in an Environmental Exposure Chamber (EEC) reproducibly evokes nasal and ocular symptoms in cat allergic patients. Mild asthmatics’ respiratory responses inside the EEC were assessed.

Methods: Patients with history of rhinoconjunctivitis and positive SPT to Fel d1 were exposed to low, well-controlled levels of aerosolized Fel d1 in an EEC for 3hrs, over 4 consecutive days (V2a, V2b, V2c, V2d). Total nasal, ocular, and asthma (cough, wheezing, & breathlessness of shortness by breath) symptoms were collected [scale=0-3] pre-EEC and then every 30min. FEV1 was measured at screening, pre- and post-EEC. Of the patients who met eligibility criteria, 12 patients were mild asthmatics, 11 patients were non-atopic asthma. Asthma scores and FEV1 from these patients were evaluated. FEV1 measures were analyzed using paired t-test.

Results: A consistent decrease in FEV1 and an exacerbation of asthma symptoms was observed in mild asthmatic patients over 4 consecutive days. At V2a, there was a decrease of 10.9 to 87.14±6.4±5.2% (p<0.05) in % predicted FEV1 with decreases of 10.2 to 87.14±5.25% (p<0.07) [V2b], 11.9 to 84.9±5.50% (p<0.05) [V2c], and 12.2 to 85.3±5.50% (p<0.05) [V2d]. Asthma scores showed consistent increase over 4 consecutive visits with mean maximum asthma scores between 3.4 to 3.7 units.

Conclusion: Low-dose aerosolized cat allergen EEC model provides a safe, controlled and natural environment to exacerbate a clinical response in asthmatic patients indicating that the EEC model may be used for testing putative therapeutics for cat allergy induced asthma.

P4075
Tuberculin skin test sensitivity in asthma patients
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Aim: The aim of this study was to evaluate the tuberculin reaction which develops with Tb type 1 immune reaction in asthma in which Th2 type immune reaction is dominant.

Material and method: This study included 36 cases with allergic asthma, 64 cases with perennial allergenic asthma and 51 cases without asthma. Tuberculin skin test was applied with Montoux method to all cases and induration diameter developed after 72 hours was recorded as millimeter.

Results: Tuberculin positivity was significantly different between cases with asthma and cases without asthma (p<0.05). The tuberculin induration diameter was calculated as 10.9±6.04 mm in cases with asthma and 15.3±5.95 mm in cases without asthma. The difference between them was significant (p<0.05). There was no significant relationship between tuberculin induration diameter and BCG scar (p<0.05).

Conclusion: While the tuberculin skin test results are evaluated presence of allergic diseases should be taken into consideration.

P4076
Multiplexed IgE determination in relation to asthma, exhaled NO and bronchial reactivity: Results from a population based survey
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Background: IgE sensitization is an important risk factor for the development and management of asthma. The aim of this study was to investigate the IgE antibody profile for a broad spectrum of allergen molecules in asthmatic patients.

Methods: Participants from the European Community Respiratory Health Survey II (n=667) were tested with ImmunoCAP IS AC against 103 allergen molecules. Bronchial reactivity was measured with methacholine test and bronchial inflammation with FENO0.05.

Results: A total of 50.7% of the controls and 80.2% of the asthmatics were sensitized against at least one food, pollen, furry animals, mould or latex allergen (p<0.0001). Asthma and increased FENO0.05 were independently related to IgE against pollen and perennial inhalated allergens, while bronchial responsiveness was only independently associated with perennial allergens. Sensitization against perennial allergens was associated with asthma (OR 3.6 CI 95% 1.2-10.6) and bronchial responsiveness. Sensitization to food allergens was related to asthma and increased FENO0.05 only if IgE against pollen and/or perennial allergens were present. Simultaneous sensitization to perennial, pollen and food allergens involves the highest risk for asthma (OR 14.7 CI 95% 7.1-30.5), bronchial inflammation and responsiveness.

Conclusion: FENO0.05 values, bronchial responsiveness and risk for asthma increase with multiple sensitization to different allergen groups. IgE against food allergens increases the risk for asthma and increased FENO0.05 in subjects with simultaneous sensitization to pollen and/or perennial allergens.

P4077
Experience of applying flow cytometry to analyze immune cells in saliva from COPD patients
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The objective was to analyze the composition of immune cells in saliva from smoking patients with early forms of COPD employed at the radiochemical facility. A group of patients with early forms of COPD (144 individuals) employed at the radiochemical facility are under the constant follow-up for the recent ten years, in addition to 264 individuals without signs of COPD, but smokers, matched to the main group by age, gender, working conditions, smoking index and history. The study included 23 individuals from the main group and 10 individuals from the group of comparison. Leukocytes were measured in saliva, mean 2.4±10/ml.

Cell viability was determined using 7-AAD. A subpopulation of immunocytes was counted in viable cells expressing a marker, CD45. There were no significant differences in total leukocytes and cells expressing markers of granulocytes (CD13+) in saliva between COPD patients and the group of comparison, the CD13+ cells amounted to 0.36% in the main group and 0% in the group of comparison. There was a significant increase in CD3+CD4+ cells (25.85 vs 1.4% in the control group, p<0.049), and CD3+CD4+ (3.3 vs 0.6%, p=0.049) in COPD patients, which proved an increase in total T-lymphocytes and T-helpers without any increase in cytotoxic cells in mucosal/salivary region, which is constantly exposed to tobacco smoke in smoking patients with COPD. The obtained findings allow assuming involvement of CD3+CD4+ lymphocytes in pathogenesis of inflammatory alterations in COPD.
P4079
Health related quality of life and sense of coherence in adolescents with asthma

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Aim: To prospectively study adolescents with asthma in transition from child to adult with respect to Health Related quality of life “HRQOL” and Sense of Coherence “SOC”.

Methods: Teenagers with asthma (n=156) were screened employing spirometry, bronchial challenge, skin prick test and exercise test at the time of referral and after five years. They completed the “Living with Asthma Questionnaire” and the Sense of Coherence “SOC” instrument. Discontinuous to moderate asthma were assigned randomly to an adult asthma clinic or to primary care.

Results: At both time-points the HRQOL of the men was better than that of the women (p<0.001). HRQOL improved for both men and women after five years. Lung function, atopy, bronchial hyper-responsiveness did not exert any impact on HRQOL or SOC. However poor adherence to the recommended asthma treatment was associated with lower HRQOL (OR= 0.29; 95% CI= 0.11-0.73; P<0.01). Young women who exercised regularly exhibited better HRQOL than those who did not (p<0.001). Only women with severe asthma demonstrated a poorer HRQOL. Over the five year period the men showed a significant stronger SOC compared to the women (p<0.05). Lung function and SOC remain stable regardless of the randomization to an asthma clinic or to primary care.

Conclusion: The HRQOL of adolescents with asthma improves with age. Young men with asthma have stronger SOC compared to young women. Adolescents with mild-to-moderate asthma receive appropriate care in the primary care system. The negative impact of poor adherence to asthma treatment on HRQOL emphasizes the importance of healthcare programs including patient education and support for adolescents with asthma and with special attention to young women.

P4080
Quantitative assessment of cysteinyl leukotrienes in human sputum during the allergen-induced asthmatic response and the effect of GSK2190915, a 5-lipoxygenase activating protein (FLAP) inhibitor

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Accurate measurement of the cysteinyl leukotrienes (cLTs) LTC4, LTD4, and LTE4 in human sputum may be useful for assessing airway inflammation. GSK2190915 is a potent FLAP inhibitor that inhibits the synthesis of cLTs. The objective of this study was to assess the effect of GSK2190915 on the production of cLTs in human sputum using ultra pressure liquid chromatography-mass spectrometry. In this double-blind, placebo-controlled, crossover study subjects took 100mg GSK2190905 and placebo orally once daily for 5 days, in randomized order. On Day 3 they had an induced allergen challenge and on Days 4 and 5 they had induced sputum collection. Sputum was frozen at ~80°C until measurement. For analysis, 200-500μL of sputum supernatant was diluted into 1mL of water spiked with [14C]LTE4 internal standard and was extracted using an Empore C-18 solid phase extraction disk prior to analysis. The limit of detection for each analyte was 1pg/mL. LTD4 and LTE4 were detected in the five year period the men showed a significant stronger SOC compared to the women (p<0.05). Lung function and SOC remain stable regardless of the randomization to an asthma clinic or to primary care. The negative impact of poor adherence to asthma treatment on HRQOL emphasizes the importance of healthcare programs including patient education and support for adolescents with asthma and with special attention to young women.

P4081
Churg Strauss syndrome associated with montelukast treatment – Study case

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Aim: To report a case of Churg Strauss Syndrome associated with montelukast treatment.

Methods: We reviewed medical records of inpatients with Churg Strauss Syndrome (CSS) treated at our hospital. The patient was a 62-year-old female with a 20-year history of moderate asthma treated with Fluticasone/Salmeterol (50/500) for 5 year and Montelukast (10mg) for 5 month (had not been on steroid treatment other than inhaled with no decreasing of steroid dose). The patient was admitted in our hospital in December with malaise, fever, headache, wheezing, musculoskeletal and thoracic pain, rhinitis and gastrointestinal. A chest radiograph showed only few reticulonodular infiltrates. Chest CT revealed infiltrates in right superior lobe. The blood eosinophilia was 52% of her total WBC count. Bronchoalveolar lavage showed 14.6% eosinophils; medullar biopsy revealed central eosinophilia. The gastric intestinal biopsy show eosinophil infiltration. Serum IgE level was elevated. The patient has more than four of the six diagnostic criteria (developed by ACR in 1990) for Churg Strauss syndrome. We believed that Montelukast use was associated with CSS. Discontinuation of Montelukast and association of oral Prednisone (1mg/kg) generated rapid improvement of the symptoms and favorable outcome. Respiratory physicians need to evaluate the risk of CSS when treating patients with LTRA. But Montelukast has been associated with CSS in a very small number. The efficacy, lack of major side effects and easy administration make Montelukast a good alternative in asthma management.

P4082
Age-specific background in inpatients with severe asthma exacerbation

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Background: Characteristics resulting in inpatients with severe asthma exacerbation remain unclear. It is considered that characteristics and risk factors in inpatients with severe asthma vary depending on age. However, they are rarely investigated.

Objective: We investigated the differences in characteristics and risk factors in different age groups. We clarified the countermeasures for each age group, and aimed to reduce the number of inpatients with severe asthma exacerbation.

Methods: All asthma inpatients who were hospitalized with SpO2 <90% (on room air), the breathless at rest, the increased respiratory rate and pulse rate >120/min between 2007-2009 were investigated. We compared their characteristics among the young age group, middle age group, and advanced age group.

Results: The total number of severe asthma exacerbations was 75. In the young age group, 55.6% has mild asthma before hospitalization. The group had poor treatment adherence, a high rate of smoking, and a high percentage of severe asthma exacerbations. The percentage of continuous ICS users in the group was 22.2%. In the middle age group, 54.8% has severe asthma before hospitalization. The group had high rates of aspirin-intolerant asthma and chronic sinusitis. The percentage of continuous ICS users in the group was 61.3%. In the advanced age group, high rates of hypertension/heart disease and diabetes mellitus were observed. The group had good treatment adherence. The percentage of continuous ICS users in the group was 82.4%.

Conclusions: The characteristics and the risk factors in inpatients with severe asthma vary depending on age. We need to establish countermeasures for asthma exacerbation according to the characteristics and risk factor depending on age.

P4083
Is it useful CD4+/CD103+/CD4+ ratio for the diagnosis of lung sarcoidosis?

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The diagnosis of lung sarcoidosis relies in part on the observation of alveolar CD4+ cells and the demonstration of an increased CD4+/CD8+ ratio. This ratio has been proposed as a diagnostic tool for pulmonary sarcoidosis. But this anomaly is also found in other lung diseases too. The search for other pathognomonic criteria allowing the discrimination of sarcoidosis patients (pts.) from patients with CD4+ alveolar lymphocytosis has been disappointing.

We investigated CD103 molecules on the T lymphocytes subpopulations. The expression of these molecules was examined on BAL lymphocytes from sarcoid patients with different radiological stages (Ist. – 23 pts; II – 16 pts; III – 9 pts.). For all patients, the expression of CD3, CD4, CD8 and CD103 was assessed by flow cytometry.

We found that CD4+/CD8+ ratio in stage 1 was 6,5±4,1; II st. – 4,5±2,3; III st. – 4,1±3,3; Lefgren’s syndrome – 8,6±4,9 and other lung disemination – 1,9±1,7. CD4+/CD103+CD8+ ratio in I st. – 0,2±0,1; II st. – 0,2±0,1; III st. – 0,1±0,1; 0,4±0,2 respectively. CD4+CD103+CD8+ ratio differ significantly (p<0.05) in all stages of sarcoidosis compared with other lung disemination while CD4+/CD8+ ratio did not.

Our findings demonstrate that the combined use of CD4+/CD8+ and CD4+CD103+CD8+ ratios provides a highly sensitive indicator of lung sarcoidosis in patients with other CD4+ BAL lymphocytosis.
**P4084**

**Premenstrual asthma and leukotriene variations in the menstrual cycle**

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Several authors report an increase in leukotriene C4 in the premenstrual phase in women with severe premenstrual asthma, indicating that anti-leukotrienes could be used in treatment.

**Objective:** To analyse the role of leukotrienes in premenstrual asthma.

**Methods:** A questionnaire on respiratory symptoms and peak flow during menstrual cycle was given to women of fertile age to define them as asthmatics who suffered from premenstrual asthma or not. The total degree of asthma severity (GINA 2005). PMA was defined as a clinical or functional deterioration (≥20%) in the premenstrual phase compared with the preovulatory phase. Blood samples to measure leukotriene levels were taken during the preovulatory and premenstrual phases.

**Results:** Blood samples were taken in 62 asthmatic women, 34 of whom (53.4%) presented PMA criteria with a premenstrual deterioration of between 20% and 40%. There was no difference in leukotriene C4 levels between the preovulatory and premenstrual phases in the women who suffered from PMA (1.30 ng/mL vs. 1.31 ng/mL; p=0.32) and those who did not (1.40 ng/mL vs. 1.29 ng/mL; p=0.62).

Neither were there any differences in leukotriene levels between women with or without PMA. The results were similar for each category of asthma severity.

**Conclusions:** Our data show that leukotriene C4 does not appear to be involved in the pathogenesis of premenstrual asthma, or support the use of anti-leukotrienes in the premenstrual asthma, at least with a moderate premenstrual deterioration. No differences appeared in any of the categories of asthma severity.

**P4085**

**Chronic exposure to allergen and cigarette smoke induces predominantly features of COPD**

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**Rationale:** Tobacco smoking by asthmatics correlates with disease severity and smoking is a risk factor for COPD. We previously demonstrated in a short-term mouse model that combining allergen with cigarette smoke exposure aggravated allergic airway inflammation. Here we investigated the effects of (very) long-term combined exposure to allergen and cigarette smoke.

**Methods:** 6-8-week-old male BALB/c mice were exposed to ovalbumin (OVA) or saline (PBS) twice a week, combined with air or mainstream cigarette smoke (5 times/week) for 6 months. Bronchoalveolar lavage fluid (BAL) and lung samples were processed for immunological and histological examination.

**Results:** Six months exposure to OVA/Air, PBS/smoke or OVA/smoke induced a pulmonary inflammation with increased macrophages, dendritic cells, lymphocytes and MIP-3α in BAL compared to PBS/Air exposure. OVA and/or smoke exposure induced an airway wall remodeling (goblet cells, collagen deposition) and lymphoid neogenesis. Mice exposed to OVA/Air had airway eosinophilia, which was absent or strongly reduced in the PBS/smoke and OVA/smoke groups. OVA-IgE was elevated in both OVA/Air and OVA/smoke mice, although more pronounced in the former.

In contrast, PBS/smoke and OVA/smoke exposure, but not OVA exposure induced a marked neutrophilic inflammation (134±91×10³ and 208±36×10³ versus 7.2±10³ cells in BAL, respectively; p<0.05). This neutrophilia was paralleled by increased levels of KC. Both smoke-exposed groups also had erythrocytes.

**Conclusion:** Chronic exposure to aerosol allergens in the presence of cigarette smoke results in a pathology with predominantly features of COPD, albeit limited characteristics of airway hyperresponsiveness.

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Severe asthma: Clinical features and management in Tunisia
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Chronic severe asthma (CSA) is a complex and heterogeneous condition with distinct subphenotypes leading to impaired quality of life and excessive healthcare need. Aim of the study was to describe the different subphenotypes of CSA and to assess its management in Tunisia.

Methods: The clinical data of 54 patients (1998-2011) with CSA were analysed. Three groups were identified according to the CSA WHO definition. G1: untreated CSA due to unavailability of therapy, G2: difficult-to-treat CSA due to compliance issues and inappropriate use of medicines, and G3: treatment-resistant CSA. The latter includes 2 subgroups: uncontrolled asthma despite the highest level of recommended treatment (G3a) and asthma which is controlled only with the highest level of recommended treatment (G3b).

Results: Patients are distributed as follows: G1: 27 patients (50%), G2: 8 patients (15%), G3: 19 patients (25%) including 9 cases of G3a (17%) and 10 cases of G3b (18%). Treatment included high doses of inhaled corticosteroids in all groups, long actingβ2-agonists were available for G2 and G3 but not for G1 due to absence of social coverage. Oral corticosteroids were prescribed in 18 patients (33%), among whom 50% belong to G1. Admissions in intensive care unit for severe exacerbation were recorded in 18 cases (29%) and near-fatal asthma was diagnosed in 11 cases (21%). CSA autoantibodies were allergy: 37 cases, allergic bronchopulmonary aspergillosis: 3 cases, gastroesophageal reflux: 4 cases and sensitivity to aspirin: 1 case.

Conclusion: Management of CSA in Tunisia hospitals still suffers from unavailability of appropriate therapy for an important proportion of patients, which makes recourse to oral corticosteroids more frequent than in the reported literature.

420. Experimental modulation of airway inflammation

P4091 Inhibition of collagen receptors: α1β1 and α2β1 integrins, has no impact on lymphocytes, but decreases eosinophil transmigration through human extracellular matrix and collagen I coated inserts
Stanislawa Bazan-Socha, Joanna Zak, Cezary Marcinkiewicz, Jacek Musial. 1Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland 2Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland 3Department of Biology, College of Science and Technology, Philadelphia, United States 4Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland

Introduction: T helper lymphocytes are likely to play a pivotal role in directing disease development and progression in asthma. We recently described presence of α1 and α2 integrins on blood eosinophils and α2 on blood CD4 and CD8 T lymphocytes in chronic asthma. We hypothesize that collagen receptors: α1β1 and α2β1 integrins may play an important role in cell transmigration to the sites of asthmatic inflammation.

Methods: We studied effects of functional active, mouse anti-human monoclonal antibodies against I-domain of α1 and α2 integrin subunit (Chemicon, USA) on eosinophil and lymphocyte transmigration through human extracellular matrix and collagen I coated cell culture inserts (Beckton Dickinson Falcon Cell Culture Dishes). Three inflammatory events – 3 μm pores sized by macroscopic care was taken to minimize the fabrication error, and excesses from the fabrication need. Aim of the study was to describe the different subphenotypes of CSA and to assess its management in Tunisia.

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Conclusion: Management of CSA in Tunisia hospitals still suffers from unavailability of appropriate therapy for an important proportion of patients, which makes recourse to oral corticosteroids more frequent than in the reported literature.
Critical immunoregulatory role for activin-A in human allergic asthma

Konstantinos Samitas, Giannis Paraskevopoulos, Catherine Hawrylowicz, Konstantinos Samitas, Giannis Paraskevopoulos, Catherine Hawrylowicz.

We have investigated the role of activin-A, a member of the transforming growth factor beta (TGF-β) family, in human allergic asthma. Activin-A is a potent immunoregulatory cytokine that has been shown to downregulate Th2 responses in allergy and autoimmune disease. However, the role of activin-A in human allergic asthma remains unclear.

Our findings indicate that activin-A significantly downregulates Th2 responses and enhances Th1 responses in human allergic asthma. Moreover, activin-A enhances the expression of Th1-related cytokines and downregulates the expression of Th2-related cytokines. These findings suggest a potential role for activin-A in the regulation of Th1/Th2 balance in human allergic asthma.

Cytokine levels were determined by enzyme-linked immunosorbent assay (ELISA) and flow cytometry. Immunohistochemistry was performed to examine the expression of activin-A in human allergic asthma tissues.

These findings have important implications for the understanding of the role of activin-A in human allergic asthma and may suggest new therapeutic targets for the treatment of allergic diseases.

Fluticasone propionate decreases MUC5AC expression in rhinovirus-infected NCI-H292 cells

Alexander Pukhalsky, Galina Shmarina, Tamara Vylegzhanina.

We have investigated the role of fluticasone propionate, a common corticosteroid used to treat allergic rhinitis, in the downregulation of the MUC5AC gene, which is responsible for the production of mucus in the airways.

Our results show that fluticasone propionate significantly decreases the expression of MUC5AC in rhinovirus-infected NCI-H292 cells. This effect is dose-dependent and lasts for up to 48 hours.

Cytokine levels were determined by quantitative real-time RT-PCR and immunoblotting. MUC5AC protein was measured by immunoblotting and immunohistochemistry.

These findings have important implications for the treatment of allergic rhinitis and other chronic respiratory conditions, as they suggest that fluticasone propionate may be a potential therapeutic agent for the downregulation of MUC5AC expression.

Activin-A significantly suppresses allergen-driven suppression of allergic responses and enhances Th1 responses in human allergic asthma

Sofia Touka, Ioanna Christopoulou, Maria S. Panoutsou, Konstantinos Samitas, Giannis Paraskevopoulos, Catherine Hawrylowicz.

We have investigated the role of activin-A, a member of the transforming growth factor beta (TGF-β) family, in human allergic asthma.

Our findings indicate that activin-A significantly downregulates Th2 responses and enhances Th1 responses in human allergic asthma. Moreover, activin-A enhances the expression of Th1-related cytokines and downregulates the expression of Th2-related cytokines. These findings suggest a potential role for activin-A in the regulation of Th1/Th2 balance in human allergic asthma.

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These findings have important implications for the understanding of the role of activin-A in human allergic asthma and may suggest new therapeutic targets for the treatment of allergic diseases.
diet are probably linked with polyphenols that most likely reduce the occurrence of asthma complications. Our experimental work was aimed at influence of polyphenols on airway hyperactivity and allergic inflammation in experimental conditions of allergic asthma (21 days OVA sensitization) after their short- or long-term (21 days) administration. We compared the activities of polyphenolic compounds mixtures from red wine (Provinol) and red fruits (Flavin7) and polyphenolic substances - resveratrol and quercetin. The changes in reactivity of respiratory system after polyphenols administration were measured: by in vitro method; by in vivo method (used whole body plethysmograph). The degree of inflammation was evaluated by eosinophil calculation and by estimation of inflammatory cytokines IL-4, IL-5 in bronchoalveolar lavage fluid (BALF).

The results of our experiments showed that: Polyphenolic compounds Provinol and Flavin7 possess an efficient antiasthmatic activities. They cause bronchodilation and also suppress asthmatic inflammation in the airways. Quercetin and resveratrol are able to induce only acute bronchodilation without antiinflammatory effects. Our results demonstrate positive antiasthmatic effect of mixture of polyphenols. This outcome confirm the hypothesis, that may become an additional therapy in prevention of airway hyperresponsiveness in asthma subjects.

P4100 Cigarette smoke extract suppresses the maturation and function of bone marrow derived dendritic cells Maasoumeh Givi, Frank Redegeld, Gert Folkerts, Esmaili Mortaz. Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands. Chronic obstrutive pulmonary disease (COPD) is characterized by chronic airway inflammation. Cigarette smoke has been considered as a major factor in the pathogenesis of COPD. The potential role of DCs in the respiratory tract of smokers' and COPD patients is poorly understood. In aim of this study is to investigate the effects of cigarette smoke extract (CSE) on the maturation and function of mouse bone marrow. Bone marrow derived DCs were developed by culturing isolated cells by femurs of BALB/c mice in presence of GM-CSF (20 ng/ml) for 10 days. CSE was added to cells cultures for 10 days.

The surface expression of maturation and co-stimulatory markers were CD11c, MHC II, CD80, CD86, CD40 and CD83, respectively, as measured by FACS analysis. The functional capacity of DCs was measured by uptake of Dextran-FITC as measured by FACS analysis. The production of TNF-α, IL-6 and IL-12 was measured by ELISA. After 10 days of incubation with CSE, the DCs maturation was assessed by (MICHC/D83 compared to control, P<0.05) and co-stimulatory receptors (MICHC/CD86, MICH/CD200 compared to control, P<0.05). The cytokine production did not differ between the experimental groups. However, resveratrol with CSE resulted in significantly less cytokine production of DCs that had been exposed to CSE for 10 days compared to the non exposed cells. In addition, the uptake of FITC-Dextran was significantly decreased in DCs that had been exposed for 10 days to CSE. It cannot be excluded that the excretions in COPD patients might be due to a decreased maturation, development and function of DCs induced by cigarette smoke.

P4101 LNC 2011 Abstract: The effect of endothelin-1 on human basophil function in vitro

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Endothelin-1 (ET-1) has profinflammatory properties and contributes to allergic late-phase responses. As basophils play a key role in allergic rhinitis or asthma, we investigated the effect of ET-1 on basophils.

Cells were isolated from venous blood of healthy donors via magnetic cell sorting. To show ETA or ETB receptor expression RT-PCR was performed. The chemotactic effect of ET-1 [10⁻⁸ M] was analysed in modified Boyden chambers (positive control MCP-1 [10⁻⁸ M]). To explore ET-1 signalling, cells were preincubated with ET-1, showing ET-1 [10⁻⁸ M] to be most effective.

The results of our experiments showed that: Polyphenolic compounds Provinol and Flavin7 possess an efficient antiasthmatic activities. They cause bronchodilation and also suppress asthmatic inflammation in the airways. Quercetin and resveratrol are able to induce only acute bronchodilation without antiinflammatory effects. Our results demonstrate positive antiasthmatic effect of mixture of polyphenols. This outcome confirm the hypothesis, that may become an additional therapy in prevention of airway hyperresponsiveness in asthma subjects.

P4102 Resveratrol impairs the release of steroid-resistant cytokines from bacterial endotoxin-exposed alveolar macrophages (AM) in COPD

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Airway inflammation in COPD might be insensitive to corticosteroids. However, corticosteroids are recommended in COPD (GOLD stages III, IV) with frequent exacerbations. Resveratrol has anti-inflammatory properties and could be an alternative in COPD therapy. We investigated the effect of dexamethasone (Dex) versus resveratrol on the release of COX-related inflammatory mediators (IL-6, IL-8, GM-CSF, MCP1) and MMP9 from AM exposed to bacterial endotoxin (lipopolysaccharide, LPS). We compared never-smokers (NS), current smokers without airway obstruction (S) and current smokers with COPD (each n=12). Cytokines and MMP9 were measured in cell culture supernatants by ELISA.

The release of IL-8 and MMP9 from LPS-exposed AM was increased in COPD (each p<0.001), the release of GM-CSF and IL-6 was decreased in COPD (each p<0.05) and the release of MCP1 was without differences between the cohorts. Dex impaired the release of all cytokines and MMP9 from LPS-exposed AM of all cohorts, but for IL-8 and GM-CSF this effect was reduced in COPD (p<0.05). In AM of COPD there was an almost complete reduction of IL-6 release but only a partial reduction of IL-8, GM-CSF, MCP1 and MMP9 demonstrating a partial corticosteroid-insensitivity. In contrast, resveratrol almost completely reduced the release of all cytokines and MMP9 without significant differences between the cohorts. Our data provide evidence for a corticosteroid-resistance of AM-dependent inflammatory responses induced by gram-negative bacteria in COPD and thus question the utility of corticosteroids in COPD therapy. Instead, resveratrol may prove an alternative.

P4103 Endothelin receptor B (ETBR) dependent GM-CSF mRNA stabilization explains the higher efficacy of bosentan vs. ambisentan in the reduction of GM-CSF release from human airway smooth muscle cells (HASMCs)

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Introduction: TNFs and GM-CSF are pivotal in chronic inflammatory airway diseases and lung fibrosis. TNFa-systems and ETBR-dependent Endothelin-1 (ET-1) release is required for full TNFα induced GM-CSF transcription in HASMCs suggesting anti-inflammatory potential of endothelin receptor antagonists (ERA). The MAP-Kinase ERK protects GM-CSF mRNA from degradation. Ambisentan (ETAR blocker) and bosentan (dual blocker) are available for PAH therapy.

Aim: We compared the anti-inflammatory potential of bosentan vs. ambisentan. Methods: HASMC culture, qRT-PCR, ELISA

Results: TNFs and ET-1 induce transcription and release of ET-1 and GM-CSF (each p<0.05). Bosentan reduces GM-CSF release more efficiently than ambisentan (p<0.01; EC50: 4.5 vs. 11 x 10⁻⁸M; EMAX: 63.7 vs. 54.8% reduction; n=9) but both block GM-CSF transcription similarly. Specific ETBR inhibition (BQ 789) also reduces GM-CSF mRNA. Combined blocking of ET,R (ambisentan) and ERK activity (PD 098059) leads to a greater reduction of GM-CSF release than single inhibition (each p<0.05). In the presence of actinomycin D which blocks gene transcription bosentan leads to a significantly greater reduction of GM-CSF mRNA than ambisentan (p<0.01).

Conclusion: Following TNFα-induced ET-1 release, ET-R induces GM-CSF transcription and ET-R signals via ERK to protect GM-CSF mRNA from degradation. This can explain why bosentan reduces TNFα induced GM-CSF release more effectively than ambisentan. Thus, bosentan may be superior in the therapy of early stages of chronic airway diseases by preventing the establishment of inflammation.

P4104 Effect of thrombin inhibition in a murine model of bronchial asthma

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Background: Thrombin is the effector enzyme of the coagulation system with important biological functions not only in thrombosis and hemostasis but also in inflammation. The precise role of thrombin in allergy remains unknown but recently there are some reports showing that thrombin plays an important role in the pathogenesis of asthma. In addition, previously we reported that thrombin inhibitor did not improve allergic response in murine asthma model.

Objectives: To evaluate the effect of inhibited thrombin on airway inflammation and hypersensitiveness in a murine asthma model.

750s
Methods: Bronchial asthma was induced by sensitization and challenge with ovalbumin (OVA). Littermates treated with saline were used as controls. The effect of inhaled different dose of thymus was assessed by administering prior to OVA exposure. Airway inflammation was evaluated by measuring the number of inflammatory cells and the level of cytokine in bronchoalveolar lavage fluid (BAL). Airway hyperresponsiveness was measured using a plethysmograph.

Results: The levels of IgE, IL-5, and the number of eosinophils in BAL were decreased in low dose of thymus treated mice compared to saline treated mice. The degree of airway hyperresponsiveness was significantly decreased in low dose of thymus treated mice compared to saline treated mice.

Conclusion: These results suggest thymus exerts a differential effect in bronchial asthma depending on its concentration.

P4105 Efficacy of inhaled anti-IL-13 mAb in a mouse model of asthma

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Interleukin-13 (IL-13) is a prototypic Th2 cytokine and a potential cornerstone of asthma pathology. IL-13 is involved in IgE synthesis, bronchial hyperresponsiveness, mucus hypersecretion, subepithelial fibrosis and eosinophil infiltration. We assessed the potential efficacy of an inhaled high affinity monoclonal antibody (mAb) Fab’ fragment neutralizing IL-13 against allergen-induced inflammation and hyperresponsiveness. BALB/c mice were subjected to ovalbumin (OVA) exposure for 1, 5, and 10 weeks referred to as short term (ST), intermediate term (IT) and long term (LT) protocols respectively. The antibody was administered as an aerosol雾200 g/kg by intubation in a tower air-flow system. In a one-week OVA-exposure model (ST), we assessed the effectiveness of different doses of anti-IL-13 (0.5 to 5 mg/ml). We report a dose-dependent increase of the anti-inflammatory effect reaching a maximum at a 5 mg/ml Airway responsiveness to methacholine was measured by using the flexVent system.

In the different protocols used in this study, administration of the anti-IL-13 Fab’ by inhalation significantly decreased bronchial responsiveness to methacholine, BALF eosinophils, subepithelial cell infiltration in lungs and airway walls, bronchial peribronchial collagen deposition and smooth muscle hyperplasia. After 1 and 5 weeks of allergen exposure (ST and IT), levels of pro-inflammatory mediators IL-13, KC and IL-6 were significantly lower in lungs from mice treated with the IL-13 neutralizing antibody. In conclusion, our data generated in a rodent model suggest that inhaled anti-IL-13 Fab’ could represent a novel and effective therapy for the treatment of asthma.

P4106 Effects of corticosteroid and montelukast treatment on distal lung parenchyma and airway walls in inflammation in guinea pigs with chronic allergic inflammation

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Rationale: The effects of montelukast or dexamethasone in asthma pathophysiolo- gy are barely understood. Aim: Airway inflammation was evaluated in distal lung parenchyma and airway walls in guinea pigs (GP) with chronic allergic inflammation. GP were inhaled with ovalbumin (OVA) group-2x/week/4weeks). After 4th inhalation, GP were matured with lipopolysaccharide in the presence or absence of supernatants of bioactivity was done with human monocyte derived dendritic cells (DCs) that were matured with lipopolysaccharide in the presence or absence of supernatants or fractions. The expression of the costimulatory molecules CD80, CD86, CD80 and CD107a was then assessed by flow cytometry.

Results: 15 supernatants from 50 strains significantly reduced both CCL17 secretion of KM-H2 and LPS-induced upregulation of DC markers. The immune modulatory activity in the screening assays applied. Furthermore, the HIV-1 co-receptor was preliminary indication of the chemical nature of one soluble probiotic compound with in vitro immune modulatory effects.

P4108 The effect of M. tuberculosis chaperonin 60.1 on leukocyte migration

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We have shown that M. tuberculosis Cpn60.1 inhibits allergic lung inflammation and bronchial hyperresponsiveness in mice (Riffo-Vasquez Y et al. Clin Exp All. 2008). Here we have evaluated the effect of Cpn60.1 of probiotic supernatants on lung eosinophils and leukocytes in vivo. BALB/c mice were immunized twice with ovalbumin (ova, 10μg/mouse i.p. in alum). From day 14 all mice were exposed to ova (3%) once daily for 3 days and Cpn 60.1 was given i.n.15 min earlier. Lung lavages were performed 24 h after the last exposure. To examine the recruitment of cells in the microvasculature of the cremaster muscle, Cpn60.1 at 1μg/mouse was given s.c. into the scrotal sac of ova-sensitized mice followed by 10ng of otxin 10 minutes later. Four hours later the animals were prepared for intravital microscopy. Cpn60.1 at 0.001-1 μg/mouse inhibited the migration of eosinophils into the airways (4a 4.3±3 vs vs 0α0.01: 1.1±1.2; 3.3±3.4: 1.3±1.4 and 9.4±2.2 x 107/ml; n=10 for 0.001-1 μg of Cpn60.1 respectively, p< 0.05). Four hours after eotaxin injection, saline treated mice showed a significant accumulation of cells in the extra vascular tissue (saline: 4.0±2 vs Cpn60.1: 2.3±1 cells/50 μm², n=6) and higher number of cells rolling along the vessel wall in 30 sec (saline: 12±1.12 vs Cpn60.1: 2.8±1.02) compared to Cpn60.1 treated mice. In contrast, the adherence of cells to the endothelial layer was higher in Cpn60.1 compared to saline treated mice (saline adhesion: 15.4±1.7 vs Cpn60.1: 22.4±4.8 cells/50μm², n=6) Cpn60.1 inhibits leukocyte migration to the lung in response to ova and prevented leukocyte rolling along and transmigration across the vessel wall in vivo.

P4109 Expression of hyperoxidized peroxiredoxin is enhanced in peripheral blood mononuclear cells of bronchial asthma patients

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Background and objectives: Increased oxidative stress is related to the pathogen- esis of asthma. Peroxiredoxin (Prx), ubiquitously antioxidant enzymes, also termed thioredoxin peroxidases. However, its role in the allergic inflammation remains unidentified. The present study investigates the expression and possible role of Prx and hyperoxidized Prx (Prx-SO3) in bronchial asthma patients.

Methods: At first, the expression of Prx and Prx-SO3 in peripheral blood mononuclear cells (PBMCs) of asthma patients were semi-quantitatively measured by using Western blot methods from asthma patients and control subjects. And then, to evaluate if higher sensitivity to oxidative stress exposure exists in PBMCs from asthmatics, intracellular ROS levels with hydrogen peroxide treatment were also determined by flow cytometry.
Results: The levels of Prx-SO3/Prx in PBMCs of asthma patients were signifi-
cantly higher compared to those in normal subjects and were also related with asthma severity. Furthermore, the intracellular ROS after hydrogen peroxide treat-
ment were remarkably enhanced and prolonged in multivariate risk factors, while transiently increased intracellular ROS levels were observed in control subjects.

Conclusions: The hyperoxidation of Prx may be related with increases suscepti-
bility to oxidative stress and possibly play a role in the pathogenesis of severe asthma.

LSC 2011 Abstract: P2Y2 receptor regulates VCAM-1 membrane and soluble forms and eosinophil accumulation during lung inflammation


ATP has been defined as a key mediator of asthma. In this study, we evaluated lung inflammation in mice deficient for the P2Y2 purinergic receptor. We observed that eosinophil accumulation, a distinctive feature of lung allergic inflammation, was defective in OVA-treated-deficient mice compared with OVA-treated wild type animals. Interestingly, the upregulation of VCAM-1 was lower on lung endothelial cells of OVA-treated P2Y2-/- mice compared with OVA-treated wild type animals. Adhesion assays demonstrated that the action of ATP on leuko-

cyte adherence through the regulation of endothelial VCAM-1 was abolished in P2Y2-deficient lung endothelial cells. Additionally, the level of soluble VCAM-1, reported as an inducer of eosinophil chemotaxis, was strongly reduced in the bronchoalveolar lavage fluid (BALF) of P2Y2-deficient mice. In contrast, we observed comparable infiltration of macrophages and neutrophils in the BALF of LPS-aerosolized P2Y2+/- and P2Y2-/- mice. This difference could be related to the much lower level of ATP in the BALF of LPS-treated mice compared with OVA-treated mice. Our data define P2Y2 as a regulator of membrane and soluble forms of VCAM-1 and eosinophil accumulation during lung inflammation.

421. Respiratory epidemiology: quality of life, therapy and socioeconomic

Late-breaking abstract: Postmenopausal hormone replacement therapy is associated with increased asthma hospitalization

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Introduction: A previous study of the Danish National Health Service Database showed that Ever using HRT was positively associated with asthma hospitalization (hazard ratio (HR)=1.49; 95% confidence interval (CI):1.35-1.63). Aims: To investigate, for the first time, the association between HRT use and risk of severe asthma exacerbations requiring hospitalization in a prospective study. Methods: We observed 446 (1.9%) incident asthma hospitalizations in 23 138 women over 9.9 years mean follow-up. 11 575 (50.0%) women ever used HRT. Ever using HRT was positively associated with asthma hospitalization (hazard ratio (HR)=1.49; 95% confidence interval (CI):1.35-1.63). The risk was highest with the longest duration of HRT use (≥ 10 years: 1.51 [1.15-1.98], 3-10 years: 1.34 [1.05-1.72], < 3 years: 1.29 [1.01-1.67], reference never users). Effect modification was detected in women without anxiety (OR=1.00; 95% CI:0.87-1.17) and those who had an asthma hospitalization in combination with anxiety in relation to the reporting of dyspnoea was not well studied.

Objectives: To study the association between reduced lung function and dyspnoea, and how anxiety affects this association.

Methods: We analysed data on 5267 women and 5066 men who participated in the Lung substudy of the Nord-Tröndelag Health Study in 1995-97. In a cross-

sectional design we used logistic regression to calculate multivariably adjusted odds ratios (ORs) for dyspnoea associated with levels of FEV1% predicted and anxiety (measured by the Hospital Anxiety and Depression scale).

Results: Among women with FEV1 ≥70% predicted, those who had anxiety had an OR (95% confidence interval) for reporting dyspnoea when walking of 2.00 (0.68-5.90) compared to those without anxiety. Using the same reference group (FEV1 ≥70% predicted and no anxiety), women with FEV1 60-69% predicted had an OR of 1.24 (0.80-1.94) without anxiety and 2.77 (1.32-5.80) with anxiety. The corresponding ORs among men without and with anxiety were 1.00 (reference) and 1.23 (0.78-1.98), 1.15 (0.68-2.01) and 2.07 (1.08-4.02), respectively. The ORs for reporting dyspnoea at rest and waking up by dyspnoea showed similar patterns in both women and men.

Conclusions: Reduced lung function in combination with anxiety had a stronger association with dyspnoea than reduced lung function alone.

Functional health status and satisfaction with health in a population reporting a participation or activity limitation: Focus on COPD

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Background: Symptoms associated with COPD can result in participation and activity limitations as well as reduced quality of life.

Objectives: To examine the impact of COPD on functional health status (FHS) and satisfaction with health (SWH) in persons with a participation or activity limitation among a national sample of Canadians.

Methods: This survey used data from the 2006 Participation and Activity Limitation Survey (PAL3), a complex population survey of Canadians reporting a disability on the census. COPD was defined present if there was a diagnosis of COPD, emphysema, or bronchitis as the cause of disability. FHS was assessed using the Health Utility Index (HUI-3) and categorized as high, moderate, or severe. SWH was categorized as high, moderate, or low. Analyses were weighted to the population and bootstrapping used to estimate variances.

Results: The sample represents 5,185,980 adults with participation or activity limitation. Subjects without missing data (55%) for the variables of interest were included. COPD was reported as the reason for disability in 1.4% of the popu-

lation. Among those reporting COPD, 44% reported moderate and 49% reported low SWH. FHS was moderately impaired for 31% and severely impaired for 46%. After adjustment, COPD was significantly associated with a lower SWH (p<0.05), but not with FHS (p=0.12).

Conclusions: While FHS was similar to the overall population with a disability, persons with COPD had a much lower level of SWH, suggesting the need to focus on quality of life enhancement strategies.

Lung function decline predicts disability in valued life activities, which in turn predicts impaired quality of life in COPD

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Background: Interrelationships among lung function, disability, and health-related quality of life (HRQL) in COPD need clearer delineation.

Methods: We carried out baseline/follow-up interviews, spirometry, and 6 minute walk tests (6MWT) for 466 participants in a COPD cohort (42% male; age 59±6; median follow-up 2.1 years). Valued Life Activities (VLA) disability was scored with a validated instrument; VLA increased disability (VLA-ID)=0.5 standard deviation increase in score baseline-follow-up (14.6% disability). We assessed respiratory-specific HRQL with the Airways Questionnaire 20-Revised. Logistic regression (including age, sex, height) estimated risk by change in absolute values of FEV1 and 6MWT for VLA-ID: linear regression (including the same covariates, VLA-ID, and baseline HRQL) predicted follow-up HRQL.

Results: Mean decline in FEV1=91 ml; mean decline in 6MWT=37 m. VLA-ID predicted worsened HRQL (p<0.001). Although FEV1, decline predicted VLA-ID (p<0.001), neither change in FEV1 or 6MWT was associated with change in HRQL. Including FEV1 and 6MWT in multivariate models, VLA-ID retained its relationship with HRQL (1.3 point change; effect size=0.29; p<0.001).

421. Respiratory epidemiology: quality of life, therapy and socioeconomic

Lung function and anxiety in association with dyspnoea – The HUNT study

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Background: Anxiety is common among people with obstructive lung diseases. However, reduced lung function in combination with anxiety in relation to the reporting of dyspnoea is not well studied.

Objectives: To study the association between reduced lung function and dyspnoea, and how anxiety affects this association.

Methods: We analysed data on 5267 women and 5066 men who participated in the Lung substudy of the Nord-Trøndelag Health Study in 1995-97. In a cross-

sectional design we used logistic regression to calculate multivariably adjusted odds ratios (ORs) for dyspnoea associated with levels of FEV1% predicted and anxiety (measured by the Hospital Anxiety and Depression scale).

Results: Among women with FEV1 ≥70% predicted, those who had anxiety had an OR (95% confidence interval) for reporting dyspnoea when walking of 2.00 (0.68-5.90) compared to those without anxiety. Using the same reference group (FEV1 ≥70% predicted and no anxiety), women with FEV1 60-69% predicted had an OR of 1.24 (0.80-1.94) without anxiety and 2.77 (1.32-5.80) with anxiety. The corresponding ORs among men without and with anxiety were 1.00 (reference) and 1.23 (0.78-1.98), 1.15 (0.68-2.01) and 2.07 (1.08-4.02), respectively. The ORs for reporting dyspnoea at rest and waking up by dyspnoea showed similar patterns in both women and men.

Conclusions: Reduced lung function in combination with anxiety had a stronger association with dyspnoea than reduced lung function alone.
ECME: Epidemiologic study of the characteristics of women with COPD in Spain
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Background: Chronic obstructive pulmonary disease (COPD) clinical trial popula-
tions are predominantly male (~75%), thus the female population is not
so well characterized.

Aims and objectives: Determine a clinical and sociodemographic profile of women
with COPD in Spain.

Methods: Multicenter, cross-sectional, observational epidemiologic study. 379
pulmonologists from health centers in Spain recruited female patients aged
≥40 yrs, smoking history ≥10 pk-ys, current COPD diagnosis and receiving
treatment/follow-up during pulmonologist visits. Clinical and sociodemographic
data were collected during study visit. Descriptive statistics were performed.

Results: 1732 women evaluated, of which: 80.8% pulmonologist diagnosis; 46.6%
primary, 30.8% secondary education; 60.1% current, 39.9% ex-smokers; 25.5% and
43.1% with history of depression or anxiety, respectively; 78.3% 65.3%, 63.1% receiving
long-acting anticholinergic, long-acting β2-agonist/corticoid, short-acting
β2-agonists. Mean age: 61.6±10.0 yrs; body mass index, 26.7±5.1
kg/m²; time, since and age at, diagnosis, 7.5±6.4 yrs and 54.1±9.8 yrs; pre-
and post-bronchodilator FEV1/FVC, 57.5±12.3% and 57.8±12.2%; O2 satur-
ation, 93.8±3.3%; PF, 35.7±19.9; SF-12 PCS and MCS scores, 37.6±10.5 and
45.7±12.0; LCADL, total, personal care, and household, physical, leisure activities,
27.2±10.9, 6.5±2.9, 11.8±5.9, 4.5±1.6, 4.4±1.8. Median no. exacerbations in
prior year, 1.0 (P25/P75: 0.0/2.0)

Conclusions: Most women in this cross-sectional study were at an age that they
could be actively working. The average FEV1; and exacerbation history suggest
an impact of the disease on these patients’ daily lives.

Supported by Boehringer Ingelheim/Pfizer.

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The restrictive spirometric pattern is associated with impaired health-related
quality of life.

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Previous population-based studies have shown that a restrictive spirometric pattern
is present in a significant proportion of the adult population and is associated
with an increased risk in morbidity and mortality. However, whether and to
what extent this pattern is associated with impaired quality of life remains to
be determined. In this study, we used data from 6005 participants from eleven
European countries and the US who completed lung function tests and the Short
Form-36 (SF-36) questionnaire during the second ECRHS survey. We defined
the restrictive spirometric pattern as FVC < 80% predicted plus FEV1/FVC <
70% and the obstructive spirometric pattern as FEV1/FVC < 70%. Physical and
mental-component summaries (PCS and MCS) for health-related quality of life
were computed and scores transformed so that the mean was 50 and the SD 10.
Mean age of participants was 43 years (range 28 - 56 years) and 51% of them were
females. Overall, 5254 subjects (87.5%) had a normal, 415.6% a restrictive
and 336.5% an obstructive spirometric pattern. The mean PCS was 56.4, 46.9
and 47.6 for subjects with normal, restrictive and obstructive spirometric patterns,
respectively (p < 0.001). The corresponding MCS mean scores were 50.0, 50.1
and 45.7 (NS). After adjustment for sex, age, body mass index and smoking, the
restrictive spirometric pattern was associated with a -2.7 PCS deficit (p < 0.001)
and the obstructive pattern with a -2.2 deficit (p < 0.001), as compared with the
normal spirometric pattern. In conclusion, the restrictive spirometric pattern is
associated with significantly impaired health-related quality of life.

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Dyspnoea in COPD patients reported in a primary care database
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Background: Dyspnoea is a primary clinical feature of COPD [1,2]. Information
on dyspnoea recording in electronic medical record databases has not yet been
reported.

Methods: A cohort was identified in the UK General Practice Research Database
(GPRD) (01/01/2003 – 30/6/2010) with both a COPD medical diagnosis code
and spirometry (FEV1/FVC <70%) and 12months history before and after cohort
eXMIS/Read codes were used to identify and define records of dyspnoea as probable or possible (less likely associated with COPD) from cohort entry until
 censoring.

Results: A cohort of 9502 patients was identified: mean age 67 y. (SD 11),
55% males, GOLD stage I: 12%, II: 50%, III: 29%, and IV: 7%. At least one
“probable” dyspnoea code was found in 76% of COPD patients; “possible” codes
were identified in 2% of patients. Codes most frequently associated with dyspnoea
were “shortness of breath” (16% of patients) and MRC Dyspnoea Scale; 45%
patients recorded as grade 2, 34% grade 3 and 5.5% grade 4 (frequencies
based on the total cohort). Dyspnoea was more often reported by older patients
and those with more advanced disease (69% patients in GOLD stage I with “probable”
dyspnoea vs. 81% in GOLD stages II or IV).

Conclusions: Dyspnoea was reported in > 75% of COPD patients identified in
the GPRD. The high frequency of dyspnoea across all GOLD stages highlights this
symptom as a significant burden and possible unmet need in COPD treatment. MRC
Dyspnoea grade is the predominant code used, linked to the Quality Outcomes
Framework, an NHS system supporting management of selected diseases.

References:

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Symptoms experienced by COPD patients during exacerbations and their
association with healthcare utilization – EXACO study
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Background: Definitions of COPD exacerbations are symptom-based while sever-
is assessment often relies on the level of healthcare utilization.

Tuesday, September 27th 2011
Objectives: To assess symptoms associated with COPD exacerbations and their association with patients’ decision to seek healthcare.

Methods: Patients with GOLD stage ≥ II COPD participating in an observational study were assessed for symptoms and healthcare use associated with exacerbations by telephone interviews.

Results: 835 patients reported 527 exacerbations. The most common symptom was increased breathlessness, 82.2% of led to a medical consultation, visit to a hospital. Fever was the symptom most strongly associated with the decision to seek healthcare.

Frequency of symptoms reported during worsenings of respiratory state and association with seeking health care

<table>
<thead>
<tr>
<th>Symptom present</th>
<th>OR (95% CI) for seeking health care</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Onset of sputum production</td>
<td>1500</td>
</tr>
<tr>
<td>Increased sputum production</td>
<td>1159</td>
</tr>
<tr>
<td>Sputum newly purulent (or more purulent than usual)</td>
<td>1343</td>
</tr>
<tr>
<td>Onset of breathlessness</td>
<td>1408</td>
</tr>
<tr>
<td>Increased breathlessness</td>
<td>2835</td>
</tr>
<tr>
<td>Onset of cough</td>
<td>1547</td>
</tr>
<tr>
<td>Increased cough</td>
<td>937</td>
</tr>
<tr>
<td>Onset of fever</td>
<td>791</td>
</tr>
<tr>
<td>Onset of chest pain</td>
<td>810</td>
</tr>
<tr>
<td>Onset of wheezing</td>
<td>1558</td>
</tr>
<tr>
<td>Borg score (increase of 1 point)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Adjusted on age, sex, education level, COPD GOLD stage, chronic bronchitis profile, season of exacerbation, and presence of cardiovascular comorbidities.

Conclusions: Breathlessness was by far the dominant symptom of exacerbations while fever was the strongest predictor of health care access.

P4120

Medication and preventive measures for COPD in the BOLD study

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Background: High use of short-acting beta agonists (SABAs) may reflect potential risks in asthma management. A better understanding of the characteristics of high users of SABAs is critical to improve quality of care.

Objectives: To describe asthma patients with high levels of use of SABA, including clinical characteristics and medical resource utilisation.

Methods: A random sample of patients aged 16-40, with regular use of dispensed respiratory drugs (R03, ATC classification) in 2005 was selected from the French claims database (EGB). Asthma-related hospital admissions were retrieved. Patterns of use of SABAs in 2007 were described. The correlates (baseline characteristics and asthma-related variables) of using ≥ 12 SABA units in 2007 were identified.

Results: Among 2093 patients (median age = 33 year-old, 54% females), 65% were using SABAs in 2007 and 8% used ≥ 12 units during this period. These patients were more likely to have a long-term disease status (p<0.001), free-access-to-care status (p<0.01), to use higher levels of systemic corticosteroids (p<0.001), and antibiotics (p<0.001) than other patients. Higher numbers of medical visits (p<0.001) and asthma-related hospital admissions (p<0.01) were also observed in this group. Conversely, no noticeable difference appeared with age, nor with gender.

Conclusions: Many patients are still using high levels of SABAs and are possibly at risk of exacerbations. The reasons of this high use of rescue medication require a better understanding.

P4123

Ratio "inhaled corticosteroids to total anti-asthma drugs", and asthma-related hospital admissions

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Background: The inadequate use of inhaled corticosteroids (ICS) remains an issue in asthma. The ratio of ICS units to total anti-asthma medications dispensed (ICS/R03 ratio) may be useful to assess the risk of severe exacerbations, leading to asthma-related hospitalisations (ARHs). We tested this hypothesis using claims data.

Objectives: To verify in claims databases whether patients with a higher ICS/R03 ratio experience fewer ARHs.

Methods: A random sample of patients aged 16-40, with regular use of respiratory drugs in 2005 was selected from the French national claims database (EGB). Three groups were defined according to the value of ICS/R03 ratio in 2007: 0% (“non users”), ≥50% (“non users”) and ≥50% (“non users”). ARHs in 2007 and 2008 were compared between the 3 groups.

Results: Among 1812 patients (mean age=32 year-old, 54.2% females), non users, inadequate users and adequate users, were 17%, 37% and 46%, respectively. ARH rate was 0.9% (in 2007 0.7% in 2008). Patients with ARH in 2007 were more numerous (p<0.0001) among inadequate users (2.1%), compared with adequate users (0.24%) and non users (0.32%). Differences were also observed in mean ARH-induced costs: 2.16 €, 48.30 € and 3.70 € for non users, inadequate, and adequate users (p<0.0005). Conclusions were similar for ARHs in 2008. Over 80% of adequate users in 2007 remained in this group in 2008.

Conclusions: Patients with ICS/R03 ratio ≥50% experience fewer ARHs than inadequate users, suggesting improved asthma control. ICS/R03 ratio may help identify asthma patients at risk of ARHs in administrative databases.
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P4124
The pattern of use of asthma medication in adolescents and young adults: A nationwide study on 2.2 million people
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Pharmacological treatment of asthma is highly effective in controlling symptoms and improving quality of life. Within the last 15 years new drugs such as combina-
tions of ICS and long-acting beta-2-agonists (LABA) and leukotriene modifiers for treating asthma has been introduced on the Danish market. Studies have shown that these drugs have changed the pattern of prescription, but most studies on prescription pattern of asthma medication have studied selected populations or population samples.

The study aimed to identify patterns of use of asthma medication in adolescents and young adults in an unselected population.

The study population comprised all Danish individuals aged 10-40 years at January 1, 2000 (N=13,264 individuals). The population was followed until the end of 2006. From the national Danish prescription registry we collected data on all asthma medication (ATC code R03) claimed by the study population.

At every year in the study period, beta-2-agonists were the most commonly claimed drug both in number of users and number of prescriptions. The first years of the study, there was an increasing use of LABA, but after the introduction of combined ICS and LABA, the use of LABA decreased whereas there was a steady increase in use of ICS and LABA in fixed combinations. When leukotriene modifiers were introduced in 1998, usage increased rapidly the first two years and then plateaued with only a small yearly increase. The use of theophyllines more than halved during the study.

This study on the use of asthma medication in an unselected population shows a shift in the use of asthma medication, but short-acting beta-2-agonists remained the most frequently used drug.

P4125
Inhaler use among asthmatics – A cross sectional study in Alappuzha and Kottayam districts of Kerala, India
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Introduction: Asthma is an important health problem worldwide. Medications in the inhaled forms are the best therapeutic options currently available for asthma [1]. Despite the availability of a large number of inhalers, the preferred modality of treatment seems to be low [2].

Aims: 1. To find out the proportion of asthmatics using inhalers as the preferred modality of treatment.
2. To bring out the various reasons for not using inhalers among the above study group.

Materials and methods: Study subjects were asthmatics in the age group of 15 to 45 years who attended the medical camps conducted in Alappuzha and Kottayam districts of Kerala, India during the period 2006 - 2009 (n=912). A semi-structured interview schedule on the use of inhalers were administered to collect the data.

Results: 52% of the study subjects accept inhalers as the preferred choice of treatment. 36% of these respondents do not like the inhaler as they believe the inhaler is costly and feels that inhalers are difficult to carry.

Recommendations: More health awareness programmes are needed to alleviate fears and misconceptions about inhaled medications. Patients should be properly trained on correct usage of inhalers.

References:

P4126
Comparing the cost-effectiveness of a wide range of COPD interventions using a stochastic population model for COPD
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Objective: To develop a stochastic population model of disease progression in COPD that includes the impact of COPD exacerbations on health-related quality of life, costs, disease progression and mortality and allows assessment of a wide range of different interventions.

Methods: The model is a multistate Markov model with time varying transition rates depending on age, sex, smoking status, COPD disease severity, and/or exacerbation type. The model simulates COPD incidence, prevalence, (severe) exacerbations, disease progression (annual decline in FEV1% predicted) and mortality. Main outcome variables are quality-adjusted life years (QALYs) and COPD-related healthcare costs. The exacerbation-related input parameters were based on quantitative meta-analysis. All important model parameters are entered into the model as probability distributions. To illustrate potential use of the model, 10-year costs and effects were projected for three different COPD interventions, one pharmacological (ICS+LABA), one on smoking cessation and one on pulmonary rehabilitation.

Results: Compared to minimal intervention, the 10-year cost/QALY ratio of 3-year implementation was €8,300 for ICS+LABA, €10,800 for the smoking cessation therapy and €17,200 for pulmonary rehabilitation. If the maximum willingness to pay would be €20,000/QALY, the probability that the cost/QALY was lower than that varied from 38% for pulmonary rehabilitation to 100% for ICS+LABA.

Conclusions: The COPD model provides policy makers with comparable information on long-term costs and effects of interventions ranging from primary prevention to care for very severe COPD and includes uncertainty around the outcomes.

P4127
Fragmented care in asthma: Data from the French national claims database
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Background: Asthma management is a major public health issue. Little is known about the frequency of fragmented care in asthma patients. It is also unclear whether those patients induce higher levels of medical resource utilisation (MRU).

Objectives: To determine the proportion of asthma patients being prescribed asthma therapy by ≤2 different general practitioners (GPs), and the medical resource utilisation (MRU) induced by these patients.

Methods: A random sample of patients aged 16-40, with at least 3 reimbursements of respiratory drugs (R03, ATC-Classification) was identified in the French national claims database (EGIB). Among those, those with at least 2 visits with prescriptions for respiratory drugs in 2007 were selected. Fragmented medical care in 2007 was defined as receiving prescription for respiratory drugs from ≥2 different GPs.

Results: Patients’ MRU was studied according to the number of distinct GPs prescribing respiratory drugs in 2007.

Results: Among 1,809 patients (mean age = 32 year-old, 59% females), nearly 55% of patients received their respiratory therapy from ≥2 different GPs (2: 36%, 3: 13% ≥3: 6%). A salient increase in the dispensing of short-acting beta agonists in 2007 was observed with the level of fragmented care in 2007 (p≤0.001). Likewise, fragmented care was associated with free-access-to-care status (p≤0.01), more asthma-related admissions (p<0.01) and medical visits in 2007 (p<0.001).

Conclusions: Our data suggest that fragmented asthma care is not exceptional and may result in higher unscheduled MRU. The reasons of fragmented care require a better understanding to optimise the quality of care in asthma.

P4128
Productivity loss in ever-smoking COPD subjects from a general population
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Background: We aimed to estimate productivity losses of chronic obstructive pulmonary disease (COPD) in hospital- and population-based subjects with spirometric post-bronchodilator COPD, relative to a control group.

Methods: 53 COPD-cases and 107 randomly recruited individuals without COPD were included from a general population. 102 COPD patients were recruited from a hospital register. All participants were ever-smokers, 40-66 yrs of age. In 4 standardized telephone interviews we surveyed the utilization of sick leave and disability pension during one calendar year. Productivity loss was defined as number of days in sick leave or disability pension. The outcomes in a two-part regression approach were any productivity loss (multiple logistic regression) and number of days of lost productivity (multiple linear regression). The latter model included subjects without any productivity loss.

Results: The logistic regression model showed little effect of COPD when we compared the population-based COPD cases to the controls. In the linear regression model we found the increased productivity loss was significantly higher in population-based subjects with stage II, stage III and stage IV COPD (95% CI) 73 (22 - 124), 178 (49 - 308) and 249 (33 - 465) days, compared to the controls. In addition, being a woman, a 1-yr increase in age and low education was associated with an increase of 59 (15 - 103), 6 (12 - 10) and 131 (65 - 197) days of productivity loss. Similar results were found for hospital recruited COPD patients.

Conclusions: The access to sick leave and disability pension was similar in subjects with and without COPD. The exclusion of these variables may result in considerably higher in subjects with COPD and was also associated with disease severity.

TUESDAY, SEPTEMBER 27TH 2011
Rural residence p=0.8 1.94 (0.7–4,9) 4.9 (1.6–15.0) 2.5 (0.9–7.4)
Number of siblings

Lâm Hoàng Thi 1,2,3, Tuong Nguyen Van4, Bo Lundbäck 1,5,6, Eva Rönmark6,7.

population survey
among adults in urban and rural northern Vietnam: Results from a
Late-breaking abstract: Allergic sensitization to common airborne allergens
P4130

and/or better compliance with medical advice – in both settings (rural and urban)
diagnostic tests require time consuming arrangements with specialized centers,
usually located at a distance from family physicians’ surgeries.

Clinical status of asthmatic children and their young age are important determinants of utilization of medical care and diagnostic procedures. The effect of rural residence and family size may reflect a better maternal care over a sick child and/or better compliance with medical advice – in both settings (rural and urban). Diagnostic tests require time consuming arrangements with specialized centers, usually located at a distance from family physicians’ surgeries.

422. Respiratory epidemiology: prevalence, incidence and remission

P4130

Late-breaking abstract: Allergic sensitization to common airborne allergens among adults in urban and rural northern Vietnam: Results from a population survey

Lím Hoàng Thị 1,2,3, Tuong Nguyên Văn 4, Bo Lundbäck 1,5,6, Ewa Rönmark 7,8.

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Background: The profile of allergic sensitization and its association with allergic diseases varies between different areas of the world.

Objective: To study allergic sensitization and the association with asthma and allergic rhinitis in the northern part of Vietnam.

Methods: A sample of 1500 subjects, aged 21–70 years were randomly selected from all 5782 responders of a questionnaire survey performed in 2007-2008. The subjects underwent a structured interview, a skin prick test with 10 common local allergens (rural and urban). Diagnostic tests require time consuming arrangements with specialized centers, usually located at a distance from family physicians’ surgeries.

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Prevalence of asthma and allergies in childhood in Guadeloupe

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Aim: To carry out a screening study for chronic obstructive pulmonary disease (COPD) among the population in Pleven.

Material: We studied 2047 people, 764 (37.3%) men and 1283 (62.7%) women, aged ≥ 40 years. Exposure to different risk factors was found in 1837 (90%) of them. All studied patients filled in a specially designed questionnaire and did spirometry (with bronchodilatation for the ones with forced expiratory value – FEV1, less than 80% predicted value).

Results: We found COPD (both symptoms and spirometry data) in 14.9% of the studied population. The analysis of the data showed: sex - 21.7% of males and 10.8% of females (p=0.0001); age - 11.9% - 40-55 years and 19.3% above 55 years (p=0.0001); place of living - 13.9% urban and 18.8% country (p=0.01). The presence of risk factors was as follows: smoking (both current and former) - 23.2% (OR=12.2); occupation - 7.3% (OR=3.5); coal heating - 3.6% (OR=1.9); frequent respiratory infections - 15.5% (OR=8.28); family history - 13.2% (OR=6.94); air pollution - 2.3% (OR= 1.1); with multiple risk factors - 28.1% (OR= 14.8). Chronic respiratory symptoms were present in 84.9% of the COPD patients and in 43.6% of the people without airway obstruction (p=0.36, p=0.0001).

Conclusion: The study found COPD in 14.9% of the studied population. There was prevalence in males, age above 55 years and in people living in the country. Among the risk factors most important were smoking, frequent respiratory infections and genetic predisposition.

Prevalence of chronic bronchitis in the Middle-East and North Africa: Interim results of the BREATHE study

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Background: Few data are available on the epidemiology of COPD outside developed countries.

Prevalence of asthma in Latin American middle-aged and older adults and its overlap with diagnosis of COPD

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Objective: To evaluate the prevalence of asthma using self-reported and spirometric criteria and to analyze the overlap in asthma and COPD diagnoses.

Methods: Multicenter study (PLATINO) in five Latin America cities: Sao Paulo, Mexico City, Montevideo, Santiago, and Caracas. Individuals aged 40 + years performed pre and post-BD spirometry and answered to ISAAC. Significant reversibility was defined as a difference between post and pre-BD FEV1 or FVC; those with a 200 ml and 12% or more differences were classified as having significant reversibility.

Results: Questionnaires and pre and post-BD spirometry were available for 5,183 individuals. Out of 1,242 individuals reporting wheezing in the last 12 months, only 184 (14.8%) also had significant reversibility by spirometry. Out of 352 subjects with significant reversibility, 34.6% also reported wheezing in the last year. As a consequence, asthma by both wheezing and reversibility affected exactly 3.6% of the sample. By analyzing COPD, based on the fixed ratio criterion, and asthma by the most specific criterion (wheezing + reversibility), out of 728 individuals with COPD, only 96 (13.2%) also presented asthma. Out of the 184 individuals with asthma, 52% also had COPD. Taking these two variables together, 96 individuals, representing 1.9% of the sample, had both asthma and COPD.

Conclusion: Wheezing in the last 12 months alone does not correlate strongly with reversibility in spirometry. COPD and asthma diagnoses are mostly independent; its overlap affected only 1.9% of the sample. However, out of all asthmatic subjects, over half also presented COPD.
Objectives: The objective of this epidemiological study was to assess the prevalence and burden of COPD, chronic bronchitis and smoking in eleven countries (Algeria, Morocco, Tunisia, Egypt, Jordan, Lebanon, Saudi Arabia, Syria, UAE, Pakistan and Turkey).

Methods: A general population sample of 10 000 subjects ≥ 40yrs in each country was generated from random phone numbers. A structured interview was proposed to all subjects by telephone. Screening questions, including history of cough and spurt production, was used to identify subjects with chronic bronchitis. Individuals who smoked ≥ 10 pack-yrs and who had either chronic bronchitis or a previous diagnosis of COPD were considered to have COPD. In a subset of the study sample, assignment of COPD was confirmed by spirometry. This interim analysis assesses the prevalence of chronic bronchitis.

Results: Of 118 039 subjects contacted, 44 892 were interviewed. 978 subjects reported having symptoms of chronic bronchitis. This corresponds to a prevalence of chronic bronchitis of 2.2% (95% CI: 2.0-2.3%), ranging from 0.6% (95% CI: 0.4-1.0%) in UAE to 2.9% (95% CI: 2.1-3.7%) in Algeria. The prevalence of chronic bronchitis was higher in women (2.4%, 95% CI: 2.2-2.6%) than in men (1.8%-95% CI: 1.6-2.0%). Prevalence increased with age: 1.6% in subjects aged 40-49 yrs, 2.2% in those aged 50 to 59 yrs and 3.0% in those aged ≥ 60 yrs.

Conclusion: The prevalence of chronic bronchitis in the Middle East and North Africa seems to be lower compared to other regions of the world.

P4139

Chronic obstructive pulmonary disease in smokers with asthma

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Aim: To find out what the prevalence of COPD amongst smokers with asthma is.

Material: The study included 154 asthmatic patients - 46 (29.9%) men and 108 (70.1%) women, aged between 40 and 69 years, all of them current or ex-smokers. The patients did spirometry and filled in a specially designed respiratory questionnaire.

Results: Spirometric criteria for COPD were found in 29.9% of all patients, in 25.6% of females and 33.3% of male patients (p=0.02). The prevalence of COPD was 23.2% amongst patients aged between 40 and 50 and 32.2% in patients above 50 (p=0.01). COPD was found in 6.1% of patients with less than 20 pack-years and in 56.2% in patients with ≥ 20 pack-years (p=0.001). More current smokers had COPD than ex-smokers - 38.2% vs. 20.5% respectively (p=0.002). The risk for COPD in smokers with asthma was OR = 15.7 (95% CI 3.8 - 64.5).

Conclusions: One third of the current/former asthmatic patients above the age of 40 in coastal Bulgaria had COPD. There was no significant difference in the prevalence of COPD between men and women patients.

P4140

COPD heterogeneity: An epidemiological perspective from the PLATINO study

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PLATINO offers an opportunity to characterise COPD heterogeneity in a population-based multicenter study. 759 COPD and 4,554 non-COPD individuals were included. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes. Dyspnea, health status (HS) and physical limitations similar in non-obstructed and stage-1. COPD was characterised for potential phenotypes.

Conclusion: COPD prevalence varies across countries and different groups of COPD patients are reported in these three local epidemiological studies on COPD prevalence among Turkish population. COPD diagnosed by spirometry in two of them.

Aim: To determine COPD prevalence using spirometry and symptom based criteria in Yigilca, a town in rural area of Duzce.

Methods: The Melen Study was a cross-sectional study conducted in May and June, 2010. Study population was inhabitants of 21000 people in Yigilca. Health service of the region was supplied by six family physicians. 400 subjects from each family physician were randomly selected from electronic data base. Interviews were made by researchers face to face. The questionnaire consist of demographic and socioeconomic variables, the history items of dyspnea, cough, sputum and smoking habits.

Spirometry was performed with Vitalograph ALPHA. COPD defined as a history of dyspnea, cough or sputum production, and post-bronchodilator FEV1/FVC ≥ 70%.

Results: A total of 2298 subjects (1471 females, 827 male with a mean age of 50) were interviewed. Spirometry was performed in 1468 of 2298 participants.

COPD prevalence for adults and adults aged ≥40 years old were 4.9% and 6.7% respectively. Post-bronchodilator FEV1/FVC ≥ 70% were detected in 7.4% of 1468 participants. Sixty five percent of the study population (1495 subjects) had never smoked. Crude smoking rate of the population was 17%.

Conclusion: Although results are consistent with the literature, our study revealed a lower prevalence than other two epidemiological studies in Turkey those used spirometry in diagnose. Low levels of smoking prevalence and rural area might be effective in low prevalence.

P4142

Prevalence, relation to smoking and other factors of COPD: Evidence from population survey

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Although COPD is a leading cause of worldwide disability and mortality it remains greatly underestimated in primary health care in Russia.

The aim of this study is to provide estimates of the prevalence of COPD in Russia in relation to patterns of cigarette smoking and environmental conditions.

Methodology: Subjects aged 35-64 years old were randomly selected from multi-centre population based epidemiological study in three Russian regions with different environmental conditions were included in the analysis. Chi-squared tests and odds ratios (OR) were calculated. Multiple logistic regression was employed to analyze association between COPD and smoking patterns and environmental conditions.

Results: COPD was revealed in 12.9% of men and 15.7% of women, whereas only 50.9% of those were ever told to have any respiratory diagnosis (p<0.001).

COPD is strongly related to smoking intensity. It is 10.5 times more likely to be related to heavy smoking in men (OR=10.9, 95%CI 5.4-19.2) and 3 times women (OR=5.9, 95%CI 2.8-8.8), but also with moderate smoking (OR=4.4, 2.9-6.7) and (OR=2.6, 1.8-3.8), low (OR=2.6, 1.8-3.8) and even ex-smoking (OR=3.06, 1.9-4.9) with short quitting history. No significant relation to intention to quit revealed.

Significant relations of COPD to environmental conditions are observed: with strongest relationships to region with severe climate conditions in Russian Far East close to Polar Circle (OR=2.9, 95%CI 2.2-3.9), and Heavy Industrial region: (OR=2.2, 1.6-3.0).

Conclusion: COPD is common among adults in Russia and is mainly undiagnosed. It is strongly associated to smoking and higher cigarette consumption, but also to living area which requires further investigation.

P4143

Smoking rates in the Middle-East and North Africa: Interim results of the BREATHE study

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The BREATHE Study Group: 1Chest Department, Adnan Mendeses University, Aydin, Turkey; 2Chest Department, Ain Shams University, Cairo, Egypt; 3Department of Medicine, Lady Reading Hospital, Peshawar, Pakistan; 4Pulmonary Department, Javed Military Hospital, Abu Dhabi, United Arab Emirates; 5Pulmonary Department, Alasad University
**P4144**

**Tuberculosis status in Minoufiya Governorate, Egypt**

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**Introduction:** TB is still the most common infectious disease worldwide. In terms of incidence, Egypt is ranked among the mid-level incidence countries.

**Aim:** To provide baseline information for the assessment of the epidemiological trends and the impact of TB control interventions.

**Patients & methods:** This was a retrospective epidemiological study including all pulmonary TB patients who were diagnosed in Minoufiya Governorate, Egypt from January 2003 to December 2008. Epidemiological data, clinical presentation, and examination, radiological examination, laboratory investigations, contact investigations were acquired for all patients.

**Results:** Incidence of pulmonary TB in Minoufiya Governorate in the studied years was 5.1 per 100,000 population. A higher percentage of pulmonary TB cases was found in males (68.3%), in rural areas (83.7%), and in middle aged persons (25–54 years) 53.8%. The majority of patients were new cases (91.9%) and most patients received CAT I drugs. There was a good response to anti-tuberculous therapy with rapid DSM conversion in most cases. The cure rate at the end of treatment reached about 80%. Treatment outcome was significantly higher with ages (15–54 years) (p<0.001). Outcome was also better in males than females (p<0.05), in rural than urban areas (p<0.05), and in patients treated with CAT I drugs (p=0.05). Direct smear microscopy (DSM) was positive only in two out of 546 contacts.

**Conclusion:** Minoufiya Governorate is one of the moderately affected governorates in Egypt with chronic bronchitis and smoking in 11 countries in the Middle East and North Africa. This may have an impact on health status.

**P4145**

**Prevalence of water pipe smoking among population in the City of Mashhad (north east of Iran)**

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**Introduction:** Pulmonary tuberculosis (TB) management is vexed when spumination microscopy is negative for M.Tuberculosis in patients with positive Mantoux and symptoms/Chest X-Ray suggestive for TB, especially to decide whether to start treatment or wait for the culture results. Several studies have shown that many smear/culture-negative patients will develop a bacteriologically positive disease later.

**Aim:** To assess the percentage of ex-adultabvus treatment that has been given and to find out if it should be reconsidered.

**Methods:** We have collected data from medical records of adult patients discharged with TB diagnosis by the Sardinian reference health centers (AOUUSL of Sassari, Cagliari).

**Results:** Among smear negative patients 36% were treated after a positive culture result, 1.8% although it was negative and 42% before culture, turned out positive in positive (4.5%), and 44% (3.1%) used water-pipes and cigarettes simultaneously.

**Conclusion:** There was a negative correlation between PFT values and positive correlation between RS with duration and total smoking (p<0.05 to p<0.01). The prevalence of WP smoking in population of Mashhad was shown for the first time which showed profound effect of WP smoke on PFT values and respiratory symptoms.

**P4146**

**Epidemiology of smear-negative pulmonary tuberculosis in Sardinia (Italy)**

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423. Respiratory epidemiology: methods, definitions and phenotypes

P4149

AWARENESS OF COPD IN PORTUGAL GENERAL PRACTITIONERS, FOLLOW UP 2010
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Objective: To perform spirometries in Buenos Aires City during World Spirometry Day, analyse the findings and correlate them with the survey proposed by European Respiratory Society

Methods: 6 Vitalograph Alpha spirometers were set on 3 sites in Buenos Aires City, with technicians and physicians. On previous days, the event was communicated and promoted.

Results: 387 spirometries were evaluated, as they met the acceptability and reproducibility criteria; 133 spirometries were carried out on site 1 (shopping arcade), 119 on site 2 (theatre hall and gym hall), and 135 on site 3 (Universidad Católica Argentina). Ages ranged from 18 to 87, the mean age being 48.6. 199 men (51.8%) participated. 74% lived in Buenos Aires City. 25.8% volunteers were smokers, 36.8% former smokers and 37.4% had never smoked. 23% of evaluated participants had cough, 27% had habitual spasm, and 59% had dyspnoea with heavy exercise, 35% on fast walk, 4% on 100-meter walks, 12% on normal walking and 1% when getting dressed or undressed. 59% did not know spirometry existed, 73% had never done one (57.94%), 23 had GOLD 1, 35 had GOLD 2, and 4 Gold 3. In total, 11.4% in the smokers vs 2.6% and 6.6% in 2006, respectively. The main reported disease associated with cigarette smoking was still lung cancer (72%). Like in 2006, asthma was the most often referred disease associated with respiratory insufficiency (54%), followed by chronic bronchitis (33%). Only 38% of smokers referred they had been informed by their physician about the damage of smoking (versus 29.9% in 2006). Not different from the previous survey there was a perception that the prevalence of the disease is increasing (57%). The population related COPD to cigarette smoking and considered COPD less serious than lung cancer, cardiovascular disease and AIDS. There is a growing interest on obtaining more information about COPD. The preferred way for obtaining information changed and is now the physician (37% vs 27%) and the media (31% vs 49%).

Conclusion: COPD awareness of Portuguese population is increasing though remaining low. However there is a high interest in obtaining more COPD information, showing that there is plenty of room for further awareness programs. Supported with a grant from ALTANA Portugal-Nycomed Group.

P4151

RESULTS OF THE WORLD SPIROMETRY DAY IN BUENOS AIRES, ARGENTINA
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Objective: To perform spirometries in Buenos Aires City during World Spirometry Day, analyse the findings and correlate them with the survey proposed by European Respiratory Society

Methods: In total, 4049 (49% females) subjects were included; mean age 58 yrs, BMI 27, and 32 pack-years. The COPD prevalence in our population was 21.7%; 56.8% had no previous diagnosis, 22.8% had a diagnosis of obstructive lung disease, > 35 yrs, and at least one respiratory symptom. Age, smoking status, pack-years, BMI, dyspnoea score (MRC), and pre-and post-bronchodilator spirometry data was obtained.

Results: A total of 4 049 (49% females) subjects were included; mean age 58 yrs, BMI 27, and 32 pack-years. The COPD prevalence in our population was 21.7%; 8.3% in subjects younger than 48 years. Most patients were classified in GOLD stages I and II (36% and 50%, respectively). The number needed to screen (NNS) in order to include one patient with COPD by the absolute value of their FEV1 and suggest that only one equation should be used during the treatment of the same patient so as to avoid alterations in the treatment.

P4150

COPD IN PORTUGAL 2010, ONE STEP TOWARDS A BETTER AWARENESS
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In 2010, we conducted a second evaluation about the awareness of COPD in the Portuguese population, following a previous study in 2006. We aimed to analyze the impact on the awareness of COPD in the Portuguese population, of all the actions taken during the last four years by Gold Committee in Portugal. Using the same questionnaire of 2006, we conducted a survey in 782 randomly selected Portuguese attendants with telephone percentage of predicted in each equation, considering the percentage expected from the PLATINO equation as reference.

Results: We evaluated 759 patients with COPD, observing staging changes in 29.4% in relation to the different equations, being Knudson et al., Crapo et al. and Pereira et al. 2007 equations that showed the greatest number of changes.

Conclusion: Overall these reference equations tested may be applied indistinctly for predicting the severity of COPD, although we should reinforce that some of them, like Knudson et al. and Crapo et al., may decrease disease severity, while Pereira et al. 2007 increases the severity, when considering only the percentage of predicted values. These results fall to attention the importance of following up patients with COPD by the absolute value of their FEV1 and suggest that only one equation should be used during the treatment of the same patient so as to avoid alterations in the treatment.

P4152

EARLY DIAGNOSIS OF COPD IN A HIGH-RISK POPULATION USING SPIROMETRIC SCREENING IN GENERAL PRACTICE
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Background and aim: Under-diagnosis of COPD is a widespread problem. This study aimed to identify early stages of COPD in a high-risk population identified through general practice.

Methods: Participating GPs (n=241) recruited subjects with no previous diagnosis of obstructive lung disease, > 35 yrs, and at least one respiratory symptom. Age, smoking status, pack-years, BMI, dyspnoea score (MRC), and pre- and post-bronchodilator spirometry data was obtained.

Results: A total of 4 049 (49% females) subjects were included; mean age 58 yrs, BMI 27, and 32 pack-years. The COPD prevalence in our population was 21.7%; 8.3% in subjects younger than 48 years. Most patients were classified in GOLD stages I and II (36% and 50%, respectively). The number needed to screen (NNS)
for a new diagnosis of COPD was 4.6. COPD diagnosis was related to gender, age, BMI (p<0.001), pack-years, and cough (p<0.001), wheezing (p<0.001) and sputum production (p=0.002). A threshold of 10% pre-test risk of COPD would have reduced the number of spirometry tests by 35% although 99% of the patients with COPD would still have been identified (NNS 3.9).

Conclusions: A case-finding strategy providing screening and diagnostic spirometry to high-risk subjects in primary care identifies a large proportion of undiagnosed COPD patients, especially in the early stages of the disease.

P4153 Is spirometry screening useful for detecting undiagnosed COPD? Kass Levent, Sezer Murat, Karakase Fatma, Akkooyunlu Muhammet. Pulmonology, Bursa Uludag University, Istanbul, Turkey

In BOLD Adana study COPD prevalence was 19.3% over 40 years of age but diagnosed COPD prevalence was 10% in 2004. Screening by spirometry might improve the detection of COPD. We aimed to answer the question that what is the contribution of spirometry screening in early detection of COPD. We recruited to study adult visitors (age ≥18 years of age) to spirometry test in our hospital garden during three days between 13 October 2015–October 2016 (world spirometry day) for spirometry screening in Istanbul. We applied to the participants standard spirometry and questionnaire. 397 participant enrolled to the study. Mean age of study population was 43.9±11.8; 243 were female (61.6%) and 154 were male (38.4%). 151 were smoker (38%), 206 were nonsmoker (51%) and 40 were exsmoker (10.1%). 252 participants (63%) were over 40 years of age. Spirometry was performed in 229/252 and questionnaire was performed in 198/252 of people. In participant who were smoker and exsmoker (n=9.37% FEV1/FVC ratio under 70% were in 1294 (12%) and COPD symptoms (were positive in 41/84 (43%) people who were over 40 years of age and who have smoking history. 44/84 (33%) people (46%) have either obstruction or symptoms. The patients who have previous COPD diagnosis were 39/111 (35.1%) in smokers. In our study spirometry screening can be useful for early detection of COPD. But combined screening modalities such as questionnaires that are better than spirometry alone are necessary for identifying those who are truly at risk, and effective treatments beyond smoking cessation are needed for preventing progression.

P4154 Spirometry test quality (home vs clinic performance) in a respiratory epidemiology survey in an Italian population sample Giuseppe Sarno1, Sara Maino1, Sandra Baldacci1, Sonia Cerrai1, Martina Fresta1, Franco Martini1, Anna Angino1, Francesco Di Pede1, Giovanni Virgili1
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Background: European Commission plans to implement Health Interview & Examination Survey in order to overcome the limitations of Health Interview Surveys. Aim: To assess the influence of home location on the spirometry test quality. Methods: A sample of subjects living in Pisa (Central Italy) was selected within IMCA2 (Indicators for Monitoring COPD and Asthma in the EU) project. An questionnaire on socio-demographic characteristics, respiratory symptoms/disorders and test factors was used. The NDD EasyOne Model 2001 was used for spirometry test, at home or in clinic; at the end of the maneuvers the quality grades A/B/C indicated a reliable result, grades D/F indicated inadequate test quality. A logistic regression analysis adjusted for smoking habits, age, sex, season, cardio respiratory diseases, disability, previous respiratory medical examination and test was run to assess association between inadequate test quality and spirometry test performance location.

Results: Analyses concerned 630 (154 participants who performed spirometry (mean age:55.8±17.0; mean BMI: 26.9±4.6 kg/m2; 45.4% male):42.4% at home, 57.6% in clinic. 91.3% of subjects had grades A/B/C; 8.7% of subjects had grades D/F (63.6% of these had performed spirometry at home). Inadequate test quality was significantly associated with home location (OR=2.5; 95% CI=1.3-4.6), age ≥65ys (OR=2.3; 95% CI=1.3-4.2) and no previous spirometry (inexpert) (OR=2.7; 95% CI=1.5-5.0).

Conclusions: Although an high percentage of adequate test quality, in a respiratory epidemiological survey a special attention would be addressed when performing spirometry at home, notably in elderly and inexpert subjects.

P4155 Lower limit of normal (LLN) for lung function parameters for over 80 year-old caucasians Simone Acquarini1, Alessandro Fois2, Barbara Pitas2, Giovanni Porqueddu1,2, Valentina Spada1, Francesco Borgo1, Roberto de Marco1, Pietro Pirina1,2,2Unit of Epidemiology and Medical Statistics, University of Verona, Verona, Italy; 1Institute of Respiratory Diseases, University of Sassari, Sassari, Italy

Spirometric reference values for over 80 year-old populations have not been calculated yet. The present study is aimed at estimating the LLN equations for Caucasians.

In an ongoing clinical study, 214 subjects aged 80-88 performed valid lung function tests (according to the acceptability and reproducibility criteria of the American Thoracic Society) in 2001/2011 at the University Hospital of Sassari in Sardinia (Italy). During the clinical examination, these subjects: (i) did not report a diagnosis of respiratory diseases, symptoms of dyspnea at restproductive cough/bronchospasm, drug use for respiratory problems, and comorbidities (associated with impaired lung function) during lifetime; (ii) reported to be not smokers or to have quit smoking for ≥20 years. Past smokers with >15 pack-years were excluded. Among the 120 males and 94 females, the mean height was 162 and 151 cm, and the percentage of past smokers was 59.2 and 4.3%, respectively. The sex-age specific mean (standard deviation) of FEV1, FVC, and FEV1/FVC ratio is reported in the following table:

<table>
<thead>
<tr>
<th>Sex</th>
<th>n</th>
<th>FEV1, L</th>
<th>FVC, L</th>
<th>FEV1/FVC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>60</td>
<td>1.85 (0.61)</td>
<td>2.45 (0.65)</td>
<td>72.2 (11.8)</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>1.80 (0.80)</td>
<td>2.44 (0.96)</td>
<td>70.1 (10.5)</td>
</tr>
<tr>
<td>Females</td>
<td>40</td>
<td>1.43 (0.34)</td>
<td>1.82 (0.48)</td>
<td>77.2 (8.8)</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>1.33 (0.33)</td>
<td>1.80 (0.47)</td>
<td>81.6 (7.9)</td>
</tr>
</tbody>
</table>

On average, the FEV1/FVC ratio did not significantly decrease according to age among males (p=0.42), whereas it slightly increased among females (p=0.054). These preliminary results suggest that the reference equations obtained from younger populations cannot be used for the long-term survivors. Appropriate LLN equations will be computed when a greater sample size is reached.

P4156 Canadian prediction equation of spirometric lung function for caucasian adults 18-90 years: Results from the Canadian obstructive lung disease (COLD) study and the Canadian ECRHS study

COLD Investigators1, ECRHS Investigators2, 1 Cardiopulmonary Research Lab, University of British Columbia, Vancouver, BC, Canada; 2 Division of Respiratory Medicine, University of British Columbia, Vancouver General Hospital, Vancouver, BC, Canada

Background: There are no preexisting reference for spirometry based on a randomly selected Canadian population. Objective: To construct spirometric reference values for adults, aged 18-90 years, by combining data of healthy life-long non-smokers from two population based studies: the Canadian Obstructive Lung disease [COLD] study and the Canadian European Community Respiratory Health Survey [ECRHS] Study.

Method: Spirometric lung function data were available from 3042 subjects in the COLD study and from 2571 subjects in the Canadian ECRHS. Exploratory curves for the combined spirometric variables versus age were continuous and linear. We identified 844 [ages 40-90 years] and 812 [aged 18-44 years] healthy, asymptomatic, life-long nonsmokers to provide normative reference values for spirometry. Multiple regression models were constructed separately for self-reported Caucasian men and women for FEV1, FVC, FEV1/FVC with covariates of height, sex and age. Results: The summary for the best-fitting regression models for healthy never-smoking, asymptomatic men and women, 18-90 years old, are as follows:

| Sex     | Parameter Intercept Age Height R-square SEE |
|---------|-------------------------------------------|-----------------|---------------|
| Male    | FEV1 | -2.06961 | -0.03167 | 0.04215 | 0.56010 | 0.50586 |
|         | FVC  | -5.39383 | -0.02286 | 0.06500 | 0.47720 | 0.63557 |
| Female  | FEV1 | -1.80997 | -0.02773 | 0.03537 | 0.06490 | 0.59793 |
|         | FVC  | -4.11886 | -0.01214 | 0.05310 | 0.52160 | 0.49381 |

Conclusion: These spirometry reference equations, derived from population-based cohorts with stringently monitored lung function measurements, provides data currently lacking in Canada.

P4157 Pulmonary resistance measured by impulse oscillometry system (IOS) seems to be related to self-reported COPD and respiratory symptoms

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Background: COPD is considered to start with small airway disease, which is more sensitive technique and more closely related to respiratory symptoms. Measuring pulmonary resistance by IOS may be a more sensitive technique and more closely related to respiratory symptoms.

Aims and objectives: This study aimed at examining pulmonary resistance mea-
sured by IOS in COPD, self-reported and/or diagnosed with spirometry according to GOLD criteria.

Methods: 419 subjects (173 men/246 women), 46-78 years, who participated in a previous population-based study, were examined with spirometry and IOS (resistance at 5 Hz, resistance at 20 Hz (R20) and the difference between them (R5-R20)) and answered a questionnaire on respiratory symptoms and diseases.

Results: 77 subjects had self-reported COPD and of them 34 subjects had COPD according to GOLD criteria. Of the 342 subjects with no-self reported COPD 90 subjects had COPD according to GOLD criteria. Subjects with self-reported COPD had higher pulmonary resistance than subjects with no self-reported COPD (R5 0.400±0.32 kPa/L, R20 0.280±24 and R5-R20 0.120±072, p<0.01 for all), both in subjects with (R5 0.420±33, R20 0.280±24, R5-R20 0.140±085, p<.05 for all) and without spirometry verified COPD (R5 0.380±31, R20 0.280±24, R5-R20 0.110±068, p<0.05 for all). Respiratory symptoms, e.g. long-standing cough, were more commonly reported by subjects with self-reported than spirometry verified COPD (p<0.01).

Conclusion: Self-reported COPD is characterized by more respiratory symptoms and higher resistance measured by IOS, compared with spirometry verified COPD. High resistance may reflect early small airway disease better than spirometry.

P4158
Definition and validation of a predictive model to identify COPD patients from administrative databases
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Background: Large administrative databases are increasingly used to identify patients with specific chronic conditions. However, the best methodology for Chronic Obstructive Pulmonary Disease (COPD) is still debated.

Objective: To develop and validate a predictive model to identify patients with COPD in Lazio region (2,625,102 residents over 45) linking clinical and administrative data.

Methods: From regional hospitalizations and drug prescriptions, through record linkage, we identified patterns of specific drug use (minimum 2 prescription during 12 months) and COPD hospitalizations during a 9-year period in 428 patients with COPD, who attended an outpatient clinic in 2006, and in 2140 people without COPD (selection from outpatients’ specialized health care registry). Through a Bootrap-Stepwise procedure we analyzed COPD associated factors. We validated the algorithm through internal (cross-validation-bootstrap, jack-knife) and external validation (comparison with COPD patients with confirmed diagnosis).

Results: Prevalence of COPD was 7.8%. Factors associated with COPD were smoking status and 1.72 (1.36 to 2.17) for exacerbation score; all after adjustment for age, sex and heart disease. When investigating the separate components in the DOSE index, the HR for a unit change in the DOSE index components was 1.81 (1.52 to 2.14) for MRC; 2.27 (1.77 to 2.92) for FEV1/PEF 90.98 (0,64 to 1.49) for smoking status and 1.72 (1.36 to 2.17) for exacerbation score; all after adjustment for age, sex and heart disease. The associations with mortality for the separate components were not statistically significant when these measures were included simultaneously in the same model.

Conclusion: The DOSE index is associated with mortality in COPD patients.

P4161
Determination of COPD characteristics via unsupervised clustering of the ECLIPSE cohort
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Background: Identifying clinically meaningful groups of COPD patients is a crucial goal to explore COPD heterogeneity. We attempt to define groups using unsupervised clustering. Methods: Data from the 2164 COPD patients in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study were assessed. Using forty-one baseline variables describing demographic, clinical, quality of life, laboratory and biomarker values, twelve factors were identified via factor analysis that accounted for 61% of the variance in the data set. The variables with the highest loadings for those factors were used to define five patient groups using unsupervised clustering, and relationships to longitudinal outcomes were assessed.

Results: Demographic profiles are shown in table 1. Over three years, higher mortality was seen in Cluster 2 (characterized by higher comorbidity and BMI despite FEV1 values that were not substantially lower than other groups) and Cluster 5, characterized by more airflow limitation.

Baseline Characteristics and Longitudinal Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cluster 1 (n=117)</th>
<th>Cluster 2 (n=423)</th>
<th>Cluster 3 (n=245)</th>
<th>Cluster 4 (n=98)</th>
<th>Cluster 5 (n=321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63 (7)</td>
<td>64 (7)</td>
<td>64 (7)</td>
<td>63 (6)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>% females</td>
<td>42</td>
<td>13</td>
<td>34</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>% Current Smokers</td>
<td>25</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>FEV1/PEF</td>
<td>49 (15)</td>
<td>51 (15)</td>
<td>55 (15)</td>
<td>51 (17)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (5)</td>
<td>32 (6)</td>
<td>26 (4)</td>
<td>27 (6)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Died within 3 yrs</td>
<td>13</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Table values are means (SD) or %.

Conclusion: Unsupervised cluster analysis identified 5 groups of COPD patients
in ECLIPSE that differ in their baseline demographics and outcomes over 3 years. These may represent subtypes of COPD. Funded by GlaxoSmithKline. (EC0104960, NCT00295525)

P4162 Asthma with and without sinusitis, results from the Swedish GA2LEN study
Roelinde Middelveld 1, Astrid van Huisstede 1, Linnea Hedman 1,2, Anders Bjerg 1, Sigrid Sundberg 1, Eva Rönmark 1,2, Gert-Jan van de Laar 1,3, Pieter Hiemstra 4, Gert-Jan Braunstahl 1, 1The Centre for Allergy Research/Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; 2Department of Occupational and Environmental Medicine, Umeå University, Umeå, Sweden; 3Department of Internal Medicine, University of Gothenburg, Gothenburg, Sweden; 4Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Introduction: In order to study the consequences of having both asthma and sinusitis compared to having asthma only, four Swedish centres studied cohorts of asthmatic patients (A), and asthma+sinusitis patients (AS). The study was part of the Global Allergy and Asthma European Network (GA2LEN) survey and follow-up.

Methods: Participants in the survey were invited for a clinical follow-up visit for interviews, and measurements of lung function, fraction of exhaled nitric oxide (FeNO) and quality of life. Group allocations were based on the interviews. A was defined as self-reported diagnosis of asthma and presence of at least one asthma symptom or use of asthma medication. AS was defined as having asthma as well as at least two sinusitis symptoms, providing that nasal blockage or nasal discharge were reported.

Results: A consisted of 470 subjects (mean age 44, BMI 27, 60% females) and AS of 130 subjects (mean age 45, BMI 27, 57% females). AS had lower FEV1%pred, FVC%pred and quality of life (mini Asthma Quality of Life Questionnaire-AQLQ), compared to A. There were no differences in FeNO, FEV1/FVC1 and reported nasal allergies.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Asthma+Sinusitis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%pred (95% CI)</td>
<td>91.4 (90.2-94.3)</td>
<td>88.4 (85.5-91.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>FVC%pred (95% CI)</td>
<td>103.9 (102.4-105.4)</td>
<td>99.9 (98.6-103.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV1/FVC (%) (95% CI)</td>
<td>74.8 (71.9-77.5)</td>
<td>73.8 (71.8-75.7)</td>
<td>ns</td>
</tr>
<tr>
<td>FeNO (median, ppb (IQ range))</td>
<td>18 (12-29)</td>
<td>17 (12-32)</td>
<td>ns</td>
</tr>
<tr>
<td>MiniAQLQ 2-SD</td>
<td>6.0 (1.9)</td>
<td>5.4 (1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: We conclude that having both asthma and sinusitis results in lower lung function and lower quality of life compared to having asthma only.

P4163 Statistical cluster analysis on the BTS refractory asthma cohort
Chris Newby 1, Astrid van Huisstede 1, Arjan Rudolphus 1, Hans Zengerink 2, Gert-Jan van de Laar 1,3, Pieter Hiemstra 4, Gert-Jan Braunstahl 1, 1Department of Infection, Inflammation and Immunity, Institute for Lung Health, University of Leicester, Leicester, United Kingdom; 2Centre for Infection and Immunity, Queen’s University Belfast, Belfast, United Kingdom; 3Royal Brompton Aconsil, Royal Brompton Hospital, London, United Kingdom; 4North West Lung Centre, University of Manchester, Manchester, United Kingdom

Background: Severe asthma is no longer believed to be a single homogeneous condition but rather a heterogeneous disease possibly containing subsets of patients. A number of clustering algorithms have been carried out on various datasets of asthmatics of differing severities but few have been confirmed by follow-up studies.

Aims and objectives: To further understand these clusters, statistical analysis was carried out to determine the patterns of variation seen in a large cohort with well characterised refractory asthma (Heaney, L et al,2010).

Methods: Independent structure was determined using Bayesian factor analysis followed by statistical cluster analysis. The analysis revealed clinically relevant factors and statistical significant clusters.

Results: 4 factors were obtained from the Bayesian factor analysis. Factor 1 described lung function, factor 2 atopy, factor 3 BMI and factor 4 Inflammation. 4 clusters were found. These clusters were significant at the 0.05 level for over described lung function, factor 2 atopy, factor 3 BMI and factor 4 Inflammation.

Cluster 1, described an older group of patients with the longest disease duration. Cluster 2, a mainly female group that had late onset and high BMI. Cluster 3 described an atopic group with high blood eosinophils and low disease duration. Cluster 2, a mainly female group that had late onset and high BMI. Cluster 3 described an atopic group with high blood eosinophils and low disease duration. Cluster 4 and spumon production (0.3 95% CI:5.7.7) were more frequent in late onset asthmatics. Medications were rarely prescribed (0.07 (95%CI:10.0-0.19) in late onset asthmatics. Theophylline (0.08 (95% CI:0.04-0.89) and salbutamol (0.21 (95% CI:0.07-0.65) were rarely used in late onset asthma (p < 0.05).

Conclusions: Desired clinical outcomes may be more difficult to achieve in elderly asthmatics due to comorbid conditions, cognitive and financial status. Chronic cough with sputum is not unusual in elderly with asthma, although it is usually associated with smoking, chronic bronchitis, and several conditions in late-onset asthmatics. Risk of adverse effects of treatment increases with increasing age and often limits choice and frequency of medications; moreover theophylline and salbutamol are rarely prescribed to patients with late-onset asthma. Future studies may give better understanding of etiopathogenesis of early and late-onset asthma.

P4165 Wheezing in morbidly obese patients is not always due to asthma
Manuel Wuhrstedt 1, Arjan Rudolphus 1, Hans Zengerink 2, Gert-Jan van de Laar 1,3, Pieter Hiemstra 4, Gert-Jan Braunstahl 1, 1Department of Pulmonology, Sint Franciscus Gasthuis, Rotterdam, Netherlands; 2Department of Surgery, Sint Franciscus Gasthuis, Rotterdam, Netherlands; 3Department of Clinical Chemistry, Sint Franciscus Gasthuis, Rotterdam, Netherlands; 4Department of Pulmonology, Leiden University Medical Center, Leiden, Netherlands

Background: Morbid obesity is becoming a world wide epidemic. Morbidly obese patients are at risk for asthma.

Aim of the study: To investigate the differences in symptoms and lung function test in morbidly obese patients with and without asthma.

Methods: A group of 95 morbidly obese patients (BMI >35 kg/m², age 18-50y) was studied. Asthma was defined as the presence of reversible airway obstruction (AFEV1%) >12% and/or PCR2 methacholine of <8 mg/ml. Patients with a physician diagnosis asthma, but not fulfilling the criteria of late-onset asthma after stopping ICS were defined as “asthma-like symptoms” (asthma-l.s.).

Results: 29 patients fulfilled the criteria of asthma, 14 had asthma-l.s., and 50 control group patients. Sex, age, BMI, smoking, abdominal circumference, atopy, FeNO, FVC, DLCO, Eppworth Sleepiness Scale score, GERO questionnaire and steps a day did not differ between the groups. Patients with asthma or asthma-l.s. had significantly more symptoms (wheezing [p<0.01], coughing [p=0.001]), and significant worse AQLQ-scores (mean 5.7 points [p<0.004], 5.5 points [p<0.002] respectively) and ACT-scores (mean 1.1 points [p=0.000] and 1.0 points [p=0.015] respectively) compared to controls (AQLQ 6.5 points, ACT 0.3 points). Patients with asthma had a significantly lower FEV1 %pred (p<0.05) and FEV1/FVC (76%pred) than the group with asthma-l.s. (102%pred [p<0.01], and 83%pred [p=0.001] respectively) and the control group (97%pred [p=0.001], and 81%pred [p=0.001] respectively).

Conclusion: A significant proportion of the patients with morbid obesity and a history of asthma does not fulfill the criteria of asthma. These patients have the same symptom scores as “asthma-like symptoms” asthmatics, despite supranormal lung function parameters.

P4166 Incidence of asthma and wheeze during adolescence – The impact of study design
Linnéa Hedman 1,2, Anders Bjerg 1, Sigrid Sundberg 1, Eva Rönmark 1,2, 1The OLIN Studies, Norrbotten County Council, Luleå, Sweden; 2Public Health and Clinical Medicine, Occupational and Environmental Medicine, Umeå, Sweden

Aim: To study the impact of study design on the incidence rates of asthma and wheeze during the teen ages.

Method: In a longitudinal study about asthma and allergic diseases within the OLIN studies in northern Sweden, a cohort of school children (n=3,430) was followed annually from age 7.8yrs by completion of an extended ISAAC questionnaire. In the endpoint survey (age 19yrs) 2,861 (83% of original responders) participated. Incident cases of asthma and wheeze from age 12 to 19yrs were identified by two methods: the annual questionnaire surveys and the endpoint survey only, respectively.

Results: The incidence was consistently higher when the incidence was based on annual surveys compared to the endpoint survey only. Based on the endpoint survey, the average annual incidence of current asthma, physician-diagnosed asthma...
and ever asthma was 0.7-1.4/100/y and current wheeze was 1.5/100/y. Based on the
annual surveys, the incidence of asthma was 0.9-2.7/100/y and current wheeze
3.6-5.3/100/y. In both study designs, the incidence of asthma and wheeze was higher
among girls than boys (p-values < 0.01). At the onset, the additional cases of
current asthma identified by the annual surveys had slightly less severe asthma
than those identified only in the endpoint survey (p < 0.06).

Conclusion: The incidence and wheeze was affected by study design.
The incidence was underestimated when only baseline and endpoint data was used.
Study design and follow-up time is important to consider for comparisons of the
incidence of asthma and wheeze between studies.

P4167
Reproducibility of an asthma symptoms and rescue medication diary: Paper and AM3™ modes
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Care Analytics, United BioSource Corporation, Bethesda, MD, United States;
3Global Health Outcomes, GlaxoSmithKline, Stockley Park, Uxbridge, United
Kingdom; 4Biostatistics and Data Analysis, United BioSource Corporation,
Bethesda, MD, United States

Objective: This study investigated the test-retest reliability of a twice-daily (morn-
ing and evening) asthma symptoms and rescue medication diary within two modes of
administration: 1) paper-and-pencil; and 2) AM3™ electronic device in patients
with persistent asthma.

Methods: Prospective cross-over study where key inclusion criteria were Asthma
Control Test (ACT) scores > 16, ICS with or without LABA use, < 2 nocturnal
awakenings due to asthma (past week), and activity limitations ≤ 1 per week.
Participants were randomly allocated to complete the diary in each mode for
15 days. Spirometry was performed at randomisation, cross over, and end of
study and changes in asthma resource use were captured. Weekly percentage of
symptom-free days (SFD) and rescue-free days (RFD) were calculated using diary
study and changes in asthma resource use were captured. Weekly percentage of
symptom-free days (SFD) and rescue-free days (RFD) were calculated using diary

Results: The mean age of the participants (n=50) was 36.5 ± 12.5 years. Seventy-five
recruits were included, of which 21 had a gold standard diagnosis

Conclusion: The test-retest reliability of SFD and RFD demonstrated acceptable test-retest reliability
ICC = 0.70 based upon all three definitions of asthma stability. By comparison,
acceptable reproducibility of the percentage of RFD (ICC = 0.78) was only observed
for the electronic diary using the FEV1 stability criterion.

P4170
Systematic review of ill-health outbreaks associated with exposure to water-based metalworking fluids
N. Feni1, Y. Gaarthuis2, A.C. Bos3, N.J.J. Schloesser2, P.J. Sterk1, 1Respiratory
Medicine, Academic Medical Center, University of Amsterdam, Amsterdam,
Netherlands; 2Respiratory Medicine, Central Military Hospital, Utrecht, Utrecht, Netherlands;
3Research & Development, C-it, Zutphen, Netherlands

Background: Asthma is presently diagnosed by its clinical presentation, including
the presence of dyspnea, cough, chest tightness and wheezing (GINA). When
combined with bronchial challenge testing, asthma can be assessed with high
accuracy. Excluding asthma is the primary objective when screening for military
service. Profiles of exhaled compounds as measured by electronic nose (eNose)
could be a rapid non-invasive test for this purpose.

Hypothesis: Exhaled breath molecular profiles measured by eNose can be used to
exclude asthma in a screening setting for military recruits.

Methods: Military recruits (16-27 yr, mean 19.8; M/F 64/11) were included in a
cross-sectional study. Exhaled breath samples were measured by DiagNose eNose
(C-it, Zutphen, NL). Symptoms of asthma were assessed by validated question-
naires (Burkey et al, ERJ ‘94) and a histamine challenge test was performed.
Asthma was considered to be present when both symptoms and PC20<8 were
present (gold standard). ROC analysis was performed to assess optimal specificity.

Results: 75 recruits were included, of which 21 had a gold standard diagnosis of
asthma. ROC analysis of exhaled breath profiling resulted in an AUC of 0.70
(p=0.007).

Optimal specificity reached 89% (sensitivity 48%).

Conclusion: Exhaled breath molecular profiling using an eNose can be a suit-
able screening instrument to exclude asthma in young, otherwise healthy military
recruits.

424. Work-related respiratory diseases and
specific exposures

P4165
Exclusion of asthma for screening purposes using exhaled air molecular profiling by electronic nose
N. Feni1,2, Y. Gaarthuis2, A.C. Bos3, N.J.J. Schloesser2, P.J. Sterk1, 1Respiratory
Medicine, Academic Medical Center, University of Amsterdam, Amsterdam,
Netherlands; 2Respiratory Medicine, Central Military Hospital, Utrecht, Utrecht, Netherlands;
3Research & Development, C-it, Zutphen, Netherlands

Introduction and objectives: There is a growing awareness that smoke produced
during wildland fires can expose firefighters and populations to hazardous concen-
trations of several air pollutants. The FUMEXP Project was developed to evaluate
the potential effects of smoke emissions on firemen health.

Methods: A sample of firefighters (n=38) was submitted to spirometry and re-
responded to the SF-36 General Health Survey before the 2008 forest fire season,
and again at the end of the 2010 season. During three years (2008-2010), a subsample of 18 firefighters was tested before and after firefighting. Exhaled nitric oxide (eNO), carbon monoxide (CO) and% carbon monoxide, during prescribed/experimental air real forest fires.

Values above international recommendations were measured: PM2.5 > 1.280 μg/m³; CO >73,000 μg.m⁻³; NO2 > 4.670 μg.m⁻³; VOC values were also high.

Airway monitoring: there was a significant decrease (p<0.05) on the eNO, and a
very significant increase on exhaled CO (p=0.001), pre and post firefighting.
Predicted FEV1,F 25,F 50 e MEF were lower at the end of the Project (p<0.05).
Three questions of the SF-36 survey had scores significantly lower.

Conclusions: With the levels of exposure monitored, forest fire smoke inhalation
can cause acute and long term health effects on exposed professionals. Suggested
preventive measures include regular health evaluation, use of adequate protecting
equipment and individual monitoring devices, planning of fire-fighting shifts and
modeling of exposure.

P4166
Firefighter occupational exposures in forest fire settings – Three years of the FUMEXP project
Antonio Jorge Ferreira, Carlos Robalo Cordeiro, Pedro Ferreira, Ana Isabel Miranda, Vera Martins, Domingos Xavier Viegas, Centre of Pulmonology,
Coimbra University Medical School, Coimbra, Portugal Department of Environment and Planning, University of Aveiro, Aveiro; Portugal Association for
the Development of Industrial Aerodynamics, University of Coimbra, Coimbra, Portugal

Objectives: Aims to identify and review all previously published reports of out-
breaks of ill health due to water-based metalworking fluids (MWFs), in order to
identify aetiological risk factors for disease, and highlight areas requiring further
research.

Methods: A multidisciplinary team agreed appropriate search terms for a system-
atic literature review. From a total of 1346 titles, 35 relevant articles, relating to
29 separate outbreaks of ill health attributed to MWF exposure were selected.

Results: 17 outbreaks related to respiratory disease, 4 to skin disease, and 8 to a
combination of both. There was a peak incidence between 1996 and 2000. The
majority were from the United States, from large car manufacturing plants using a
central sump. The mean attack rate for allergic respiratory disease during outbreaks
was 5.9% of the exposed workforce. Outbreaks were identified with all types of
water-based MWFs, and mean MWF aerosol levels were below recommended
levels of exposure monitored, forest fire smoke inhalation

can cause acute and long term health effects on exposed professionals. Suggested
preventive measures include regular health evaluation, use of adequate protecting
equipment and individual monitoring devices, planning of fire-fighting shifts and
modeling of exposure.

P4170
Systematic review of ill-health outbreaks associated with exposure to water-based metalworking fluids
Clare Burton, Brian Cook, Helena Scaife, Gareth Evans, Chris Barber. Centre for Workplace Health, Health and Safety Laboratory, Buxton, Derbyshire, United
Kingdom

Objectives: Aims to identify and review all previously published reports of out-
breaks of ill health due to water-based metalworking fluids (MWFs), in order to
identify aetiological risk factors for disease, and highlight areas requiring further
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combination of both. There was a peak incidence between 1996 and 2000. The
majority were from the United States, from large car manufacturing plants using a
central sump. The mean attack rate for allergic respiratory disease during outbreaks
was 5.9% of the exposed workforce. Outbreaks were identified with all types of
water-based MWFs, and mean MWF aerosol levels were below recommended
exposure limits in most cases. For respiratory disease outbreaks, bacteria were iso-
lated in 76%, fungi in 71% and opportunistic mycobacteria in 59% of workplaces.
Endotoxin contamination of MWF ranged from non-detectable to 5.3±10³ EU/mL,
and measured airborne endotoxin levels ranged from 0.52 EU/m³ to 126 EU/m³.

Conclusions: Despite numerous investigations, significant knowledge gaps re-
main, particularly regarding the aetiology, natural history and risk factors for
these outbreaks. The available evidence supports the hypothesis that microbial
contamination is important in the aetiology of occupational lung disease in this
group, and improvements in workplace hygiene have generally been associated
with a cessation of new cases.

P4169
Conclusion: Exhaled breath molecular profiling using an eNose can be a suit-
able screening instrument to exclude asthma in young, otherwise healthy military
recruits.
Epidemiological study of the workforce after an outbreak of occupational asthma due to chromium and cobalt in an aerospace factory

Gareth Walters1, Atulastar Robertson2, Vicky Moore3, Cedde Burge1, Arun Vellorre1, Sherwood Burge1. 1Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Birmingham, United Kingdom; 2Department of Gastroenterology, University Hospitals Birmingham, Birmingham, United Kingdom

An outbreak of asthma due to chromium and cobalt in 4 employees at an aerospace factory occurred after coolant oils were changed in 2004 (6-24 month latency). The factory manufactured high chrome and nickel alloys with hard metal tipped tools containing cobalt. Oils and mist exposure met exposure standards. This prompted an investigation of the workforce, in order to measure extent and cause of outbreak. 62 (of 65) employees (n=54±18; mean age 34±5; 58% currently working with coolant oils; 58% never smoked) undertook a self-completed symptom questionnaire, lung function, urinary analysis and received expert consultation. 74.1% had urinary chromium excretion indicating occupational exposure. 66.1% had at least one respiratory symptom, most symptoms from after 2003. Clinical opinion identified cases of definite occupational asthma (OA), possible asthma (PA) and 3 with positive challenges to chrome and one with cobalt, one not challenged, symptomatic pre-existing asthma (17; 27%) and occupational rhinitis (OR) (18; 29%). All 5 OA cases and 15/18 OR cases worked with coolant oils. Employees with OA, asthma or OR were compared with asymptomatic workers (n=57). Those with OA or OR were of similar age and no more likely to be smokers, have abnormal spirometry or FeNO than controls. Those with OA and OR had significantly higher urine chromium (p=0.05) and cobalt (p=0.003) concentrations and a longer mean duration of employment. OR was more likely in those undertaking manufacturing work (p=0.006) or work with machines using coolant oils (p=0.02). Chrome exposure sufficient to cause occupational asthma can occur from metal-working fluid aerosols when machining high chrome alloys.

P4172 Past dust and gas/fume exposure and COPD in Chinese: The Guangzhou Biobank cohort study

Kin Bong Hubert Lam1, Peng Yin2, Chao Qiang Jiang3, Wei Sen Zhang3, Biobank cohort study

Past dust and gas/fume exposure and COPD in Chinese: The Guangzhou Biobank Cohort, Guangzhou Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom; 3Guangzhou Biobank Cohort, Guangzhou Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom; 2Guangzhou Biobank Cohort, Guangzhou Biobank Cohort Number 12 People’s Hospital, Guangzhou, China; 4School of Public Health, The University of Hong Kong, Hong Kong, China

Background: The impact of occupational dust and gas/fume exposure on chronic obstructive pulmonary disease (COPD) has been described in Western populations but the extent has not been quantified in developing countries.

Aims: We examined the relationship between past dust and fume exposure and prevalence of COPD and respiratory symptoms in a Chinese population sample. We have calculated the population attributable fraction for COPD due to previous occupational exposure.

Methods: Baseline data from the Guangzhou Biobank Cohort Study (2003-6; n = 8,119) were analysed. Self-reported intensity and duration of dust and gas/fume exposure was obtained from which a cumulative exposure index was derived. COPD was defined based on spirometry using lower limit of normal. Respiratory symptoms were assessed by the MRC questionnaire.

Results: In this sample (27.3% men, mean age 61.9; 68.8 years), COPD was associated with dust or gas/fume exposure in a dose-response manner with no evidence of effect modification by smoking (adjusted OR for high level exposure = 1.49; 95% CI 1.21-1.91). Similar associations were found for chronic cough/phlegm (1.60; 1.18-2.17) and dyspnoea (1.38; 1.21-1.58). The population attributable fraction for COPD due to occupational exposure was 11.2% (95% CI 1.4%-20.0%).

Conclusion: Occupational dust and gas/fume exposure is associated with an increased prevalence of COPD in this Chinese sample, independent of smoking. The magnitude is similar to that reported in other populations.

P4173 Long term effect and allergic sensitization in newly employed workers in laboratory animal facilities

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Background: Allergic reactions are common in laboratory animal workers and one of the most frequent working with laboratory animals are reported work-related allergic symptoms and may develop occupational asthma. Working in laboratory animal facilities also implies exposure to airborne dust, contaminated with microbial and other products, which may lead to health effects.

Objective: The aim of this study was to identify targets that can predict sensitization to laboratory animals. Skin Prick Test change and sensitization to laboratory animals were used as an outcome variable.

Methods: In a prospective longitudinal study newly employed personnel who were employed to work with laboratory animals at Karolinska Institutet (Sweden) were investigated before and 6, 12 and 24 month after employment. Lung function, bronchial challenges, exhaled NO and nasal lavage were performed and blood samples were taken at each visit.

Results: Seventy subjects attended all four visits and 13 of those (19%) became sensitized to laboratory animals during the study. Lung function (VC and FEV1) deteriorated (as compared with predicted values) and increased blood levels of eosinophils and IL-2 over time were observed.

An increased risk of developing laboratory animal allergy was significantly associated with female sex, atopy, symptoms, CDAI=-0.92 cell/μL blood, total IgE= 15.5 μA/L, specific IgE to rat (e57=-0.01 kUA/L) and mouse (e88=-0.004 kUA/L).

Conclusions: One of five subjects became sensitized to one or two laboratory animals in this study and atopic subjects before starting working with animals had a greater risk to develop laboratory animal allergy.

P4174 Cow hair sensitisation is uncommon among Danish dairy farmers despite high allergen levels

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Background: Bovine allergens can induce allergic airway diseases recently. High levels of cow hair allergens (CHA) in dust from stables and homes of dairy farmers were reported (Zahradnick E et al. IAAI 2011;155:225-233).

Objective: To investigate CHA levels among dairy farmers (DF), pig farmers (PF), former farmers (FF) and never farmers (NF) and to assess CHA sensitisation in these groups.

Methods: In 2007-8 415 dust samples were collected using an electrostatic dust collector, EDC (Niss 1 et al. Appl Environ Microbiol 2006;74:5621-7) with a 14 days sampling time among 54 FF, 27 DF, 71 FF and 51 NF. Among farmers sampling was carried out both summer and winter. The cow hair allergens levels (μg/m2 ) were measured using a sandwich ELISA assay (Zahradnik E et al. IAAI 2011;155:225-233). SPT for cow hair allergens (ALK-Abello ™) were performed among 48 PF, 20 DF, 54 FF and 31 NF.

Results: CHA levels were substantially higher in stables than bedrooms. DF had much higher CHA level compared to PF, FF and NF had low levels of CHA in their bedrooms compared to DF and PF. No one but one PF (former DF) was sensitised to CHA.

Conclusions: These results confirm high CHA levels on dairy farms. Despite this no dairy farmers were sensitised to CHA. Selection out of dairy farming might be of importance.

P4175 Fungal colonization of oxygen humidifier and nebulizer chambers

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Humidified oxygen and nebulizers are routinely used in hospitalized patients suffering from respiratory ailments. These can however be potential source of allergens or infection if colonized by fungi. We undertook a study to determine if the oxygen humidifier chambers of portable cylinders and central lines at our hospital were colonized by fungi. The Hudson’s chambers of nebulizers were also studied as they remain wet after use. Samples of these were obtained using sterile swabs on Tuesday as these chambers are usually cleaned on every Saturday.

Samples were taken from ICUs, wards, casualty and OPD on a single day. Air samples were also obtained on the same day to determine if the fungus spore load in the inhaled room air was normal or high. 46/53 (86.79%) swabs form oxygen humidifiers and 717 (41.17%) swabs from Hudson’s chambers grew fungi. There were a total of 14 species of fungi identified altogether of 4 of them are virulent strains and 6 are known allergens for asthmatics. The colonization was less in shallow Hudson’s chambers (35.71%) as compared with predicted values) and increased blood levels of eosinophils and IL-2 over time were observed.

Conclusions: Seventy subjects attended all four visits and 13 of those (19%) became sensitized to laboratory animals during the study. Lung function (VC and FEV1) deteriorated (as compared with predicted values) and increased blood levels of eosinophils and IL-2 over time were observed.

An increased risk of developing laboratory animal allergy was significantly associated with female sex, atopy, symptoms, CDAI=-0.92 cell/μL blood, total IgE= 15.5 μA/L, specific IgE to rat (e57=-0.01 kUA/L) and mouse (e88=-0.004 kUA/L).

Conclusions: One of five subjects became sensitized to one or two laboratory animals in this study and atopic subjects before starting working with animals had a greater risk to develop laboratory animal allergy.
**P4176**

**Prevalence of chronic obstructive pulmonary disease in male workers exposed to dust, gas and fume**

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**Purpose:** It is known that chronic obstructive pulmonary disease (COPD) can be developed after exposure to many kinds of dust, gas and fume. But the prevalence of COPD was not investigated extensively, especially after bronchodilator inhalation.

**Method:** Chest X-ray images were taken in 1,298 male workers exposed to many kinds of dust, gas and fume. Pulmonary function tests were done with short-acting bronchodilator during the periodic health examination from 2008 to 2010. Excluding the workers with the abnormal radiological findings that could affect lung function, the data of a total of 838 workers were analyzed.

**Result:** The prevalence of COPD increased with age: under age 45, 0.0%; 45 to 64, 31.6%; 65 to 74, 51.8%; 75 and over, 62.2% (p<0.001). COPD was also prevalent in those with high relative exposure index, sum of multiplication of exposure level and exposure duration: under 60, 35.5%; 60 to 99, 37.2%; 100 and over, 47.2% (p<0.009). About half of pneumoconiosis patients had COPD - 43.5% in profusion category 1; 49.6% in 2; 62.5% in 3, but the prevalence in profusion category 0/1 was also high, 30.1% and 30.8%, respectively. The prevalence of COPD in smokers was higher than non-smokers (31.8%), but there was no difference between ex- (41.7%) and current-smokers (41.5%). In ex- and current-smokers, it was 30.0% under 15 pack-years, 42.4% in 15 to 29, and 54.1% in 30 and over.

**Conclusion:** The prevalence of COPD was very high in workers exposed to many kinds of dust, gas, and fume occupationally. Also, it showed the increasing trend with exposure intensity.

**P4177**

**Occupational asthmogams and total IgE according to asthma status in the EGEA study**

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**Introduction:** The comprehension of the relationship between asthma and immunoglobulin E (IgE) remains a challenge. Several occupational asthmogams have been identified to cause or aggravate asthma, but their associations with IgE have rarely been studied.

**Aims:** To study the relationship between occupational exposure to asthmogams and total serum IgE in non-asthmatics, childhood-onset and adult-onset asthmatics.

**Methods:** Analyses were conducted in 1212 adults (aged 17-79 years, 48% men) from the Epidemiological study on the Genetics and Environment of Asthma (EGEAE, 2003-07) without missing data for work history and IgE. Lifetime exposure to asthmogams was estimated using an asthma-specific job-exposure matrix.

**Results:** 32%, 28% and 36% of non-asthmatics, childhood-onset and adult-onset asthmatics had ever been exposed to asthmogams. In non-asthmatics, exposed subjects had a significantly lower total IgE level. In asthmatics, no association was observed. Nevertheless, among women with childhood-onset asthma, exposure to asthmogams was associated with higher IgE level (adjusted OR (95%CI) for IgE>=100 IU/ml: 2.49 (1.07-5.83)).

<table>
<thead>
<tr>
<th>Total IgE, crude geometric mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non asthmatic Childhood-onset asthmatic Adult-onset asthmatic</td>
</tr>
<tr>
<td>(n=718) (n=111) (n=383)</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Occupational exposure</td>
</tr>
<tr>
<td>Never exposed or exposed to low risk agents</td>
</tr>
<tr>
<td>Ever exposed to asthmatics</td>
</tr>
<tr>
<td>p</td>
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<tr>
<td>p adjusted for age, sex and smoking</td>
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</tbody>
</table>

**Conclusion:** Our results suggest a healthy worker effect among non-asthmatics. Further analyses will be conducted by distinguishing the types of asthmogams with exposure intensity.

**P4178**

**Irritative effects of respirable particles and chromium in non-smoking welders**

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**Introduction:** Welding fumes are known to contain chromium (Cr) compounds. Chronic inhalation of Cr and other constituents of welding fume may induce inflammatory reactions.

**Aims and objectives:** We studied irritative effects of welding fume and Cr in non-smoking welders using spirometry and fractional exhaled nitric oxide (FeNO).

**Methods:** Shift exposure to respirable particles in the welding fume was measured with personal samplers in the breathing zone of 119 non-smoking welders. The Cr concentration in these fume samples was determined by inductively coupled plasma mass spectrometry. Post-shift spirometry was performed with pneumotachography. FeNO was measured with a handheld device (NIOX Mini®). A potential irritative effect of Cr and welding fume was evaluated with multiple logistic regression models.

**Results:** Lung function measurements revealed normal average values standardized to European Community of Coal and Steel. (median of forced vital capacity (FVC): 111.2%; forced expiratory volume in one second (FEV1):104.7%; Tiffeneau index (FEV1/FVC): 77%). Median of FeNO was 17.5 ppb Cr, respirable welding fume and use of dust masks together explained less than 10% of the variance of the variables under study. We found no effect of any of these potential predictors measured during a single working shift on FeNO or Tiffeneau index.

**Conclusion:** Our data analysis did not reveal an acute irritative effect of Cr and welding fumes in non-smoking welders assessed with spirometry and FeNO. Nevertheless, further investigations with the implementation of non-invasive methods to assess inflammatory processes in the upper airways are necessary to make final conclusions.

**P4179**

**Respiratory work disability and occupational outcomes in adults with asthma and bronchial hyperresponsiveness**

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**Background:** The correlation between asthma and work disability has been demonstrated in previous surveys. Changing job for respiratory problems often defines respiratory work disability. Little is known about occupations of asthmatics with respiratory work disability after they were forced to change job. This study investigates factors associated to respiratory work disability in asthmatics, focusing on occupational outcomes.

**Methods:** 342 adults in working age with asthma, diagnosed by GINA criteria and methacoline challenge or bronchodilator response, answered to a questionnaire. Subjects with occupational asthma were excluded. Respiratory work disability was defined as to have changed job/task because of asthma. Information about pulmonary function tests and skin prick tests were obtained from medical records.

**Results:** 22 subjects reported respiratory work disability. Age, sex, smoking, atopy were not risk factors for changing work. Patients with work disability referred more often uncontrolled asthma (72.7% vs 60.5%), regular use of asthma controllers (81.1% vs 66.6%) and asthma relievers, even if these differences were not significant. Workers that have changed job because of asthma were still prone to work exacerbated asthma in the last year (81.8% vs 35.3%; OR 5.75, CI 95% 1.77-18.71) and work exacerbated rhinitis in the last year (61.9% vs 31.6%; OR 2.90, CI 95% 1.07-7.02), remaining exposed to known asthmogens (63.6% vs 54.1%).

**Conclusions:** In this study atopy did not predict job change. Maybe because the current economical situation, workers with respiratory work disability did not move to more safe occupations, remaining at risk of work exacerbated asthma.

**P4180**

**Enzyme immunoassay (EIA) for bacterial peptide glycolipid (PGN) assessment in air and house dust samples**

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PGN forms the outer wall of Gram+ bacteria (GM+B) and when liberated induces inflammation through TLR2 and NLR2. Thus, PGN is a potential marker for GM+B. We employed 3 PGN standards, 3 monoclonal antibodies (mAb) and environmental samples to develop PGN-specific EIA. Reagents: anti-PGN mAb clones (B10, 6G6, 3C11); Cerebide β-D-galactoside, Keratin and Phenosin cerebrosides for PGN capture; PGN standards: Bacillus subtilis (PGN-BS), Micrococcus luteus (PGN-MI) and Staphylococcus aureus (PGN-Sa). Evaluation methods: inhibition EIA, EIA with cerebrosides for capture and PGN mAb for labeling, and double mAb sandwich EIA. Samples from three studies were extracted in PBS plus 0.05%Tween 20.

Keratin proved a higher affinity receptor than other cerebrosides. The B10 and 3C11 mAb showed high specificity for PGN-BS and PGN-MI. The 6G6 mAb...
exhibited high specificity for all 3 PGN. Sandwich EIA was not suitable for the detection of PGN because the mAb were directed toward the same epitope. Inhibition assays were inferior to the method employing cerebroside. Cerebroside effectively captured PGN for EIA. The 6% mAb bound to soluble (PGN-SA) or insoluble (PGN-Bs; PGN-MI) macromolecular PGN while mAb B10 and 3C11 bound preferentially to insoluble (PGN-Bs; PGN-MI) PGN. House dust samples had mean (±SD) PGN levels of 34.45±4.70 µg/m³. Inhaled fraction air samples averaged 7.52±2.90 µg/m³ while EDC passive air samplers averaged 2740±680 µg/m³ PGN.

These data show that our antibodies bind to an epitope on the PGN backbone that is common to many GM1β. The specificity of the cerebroside-mAb EIA is sufficient for quantitation of PGN in household dust and air samples.

P4181 Characterization of airborne organic dust exposure with limulus amoebocyte lyase activity

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The aim of the study was to evaluate if measurement of endotoxin and/or pyrogenic activity by suitable methods to describe different exposure circumstances for example in composting plants. Dust sampling was performed with stationary pumps. Filter samples were extracted with PBS. Endotoxin activity was determined with Limulus amoebocyte lysate (LAL)-assay (Charles River, Sulzfeld). Pyrogenic activity was measured with a whole blood assay (WBA) using cryopreserved blood (Zwissler Laboratorium, Konstanz) measuring Interleukin (IL)-1β release with a specific ELISA in the cell-free supernatant. In all 124 filter extracts endotoxin activity as well as pyrogenic activity were detectable. Median of endotoxin activity was 12 EU/m³ (range 6-3421). Median of pyrogenic activity was 3831 PU/ml (pyrogenic unit; 1PU/ml = 1 pg/ml IL-1β release; range 2126-124590). Correlation between LAL-activity and WBA was r=0.78 (Pearson). Dust samples collected in wheel loaders (n=33) showed median values of 9 EU/m³ and 3580 PU/ml, respectively whereas in the area of sieving machines (n=14) a median of 61 EU/m³ and 7680 PU/ml was measured. Test results of WBA and LAL assay were compared with receiver operating characteristic (ROC) curve using LAL-Test as gold standard. Presuming a desirable test sensitivity of 95% WBA provides a possible specificity of 40% for a cut-off of 10 EU/m³ increasing to 100% specificity with a sensitivity set at 500 EU/m³. (LAL)-Test and WBA are applicable methods to evaluate bioaerosol exposure. Especially in areas with lower endotoxin activity and with further pyrogenic components WBA may deliver additional information.

Bioactivity of 14C-labeled endotoxin in aggregates, shed blebs and whole bacteria: Potency comparison in the LAL assay, cell cultures, and mouse bioassay

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It is unknown if endotoxin reactivity in the LAL assay varies by its presentation or if this differences parallel reactivity in vitro and in vivo. We compared endotoxin reactivity in the LAL assay, in cell cultures and in vivo when presented in different forms.

Lipopolysaccharide (LOS) from Neisseria meningitidis sero B was metabolically labeled and incorporated into intact bacteria, purified membrane blebs, and aggregates (14C-LOSagg). 14C-LOS content of each was quantified as LOS-specific 13C-3-OH fatty acids. Equivalent escalating doses of 14C-LOS-containting bacteria, blebs, or LOSagg were tested in the LAL assay, in vivo in C3HeB/Fecl mice following intranasal installation (monitoring induced airway inflammation), and in vitro using HEK293 cells or CD14, MD-2, TLR4 (monitoring extracellular accumulation of IL-8). Doses of 14C-LOS were measured by scintillation counting (our gold standard).

Potency varied depending on LOS presentation. Ranked reactivity was: in the LAL assay, blebs > LOSagg > bacteria, by airway inflammation, bacteria > blebs > LOSagg by activation of HEK cells. LOSagg > blebs > bacteria. Differences in potency reached 10-fold for in vitro and in vivo inflammation. Across the range of doses, the ratio of LOS concentration determined by the LAL assay to the gold standard was 1.0-3.3 for blebs, 0.3-0.7 for aggregates and 0.1-0.2 for whole bacteria.

How endotoxin is presented significantly affects endotoxin reactivity in the LAL, cell cultures, whole blood bioassays and mouse bioassays. Comparing the gold standard LAL assay substantially underestimates the content of the LOS preparations for LOSagg and bacteria.

P4183 COPD causation and workplace exposures; an assessment of annual FEV1 decline significance between expert clinical raters

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Objectives: Epidemiological studies identify that 10-15% of the burden of chronic obstructive pulmonary disease (COPD) is attributable to indoor occupational exposures. Despite this knowledge, very little is known about how clinicians weight this contribution against other risks.

Methods: 15 hypothetical cases of COPD were structured to represent a broad range of smoking and occupational exposure histories. Twelve clinical experts in COPD and 12 clinical experts in occupational lung disease (OLD) were invited to rate the causes of COPD in each case. Cases were developed a priori into 9 categories; combinations of low, medium and high tobacco smoking and low, medium, and high COPD-risk occupational exposures. Five cases also contained annual FEV1 decline data, and raters were asked to comment about its significance, and any required actions. These latter five cases represented annual FEV1 declines of between 95mLs to 400mLs a year.

Results: Responses were received from 14 raters (9 OLD and 5 COPD), representing a 58% response. Significant variation was seen when assessing the relevance of various declines in FEV1. In particular, there were differences in approach to identifying significant or concerning decline, and similarly different advice concerning the risks of continuing employment.

Conclusion: There was a wide range of estimates relating to causative factors in COPD documented by experienced clinical raters, and a variance of view relating to annual decline in FEV1. An improved evidence base is required to help formulate practical guidance for respiratory and occupational physicians when interpreting serial measures of lung function in working groups.

P4184 Respiratory symptoms, lung function tests and bronchial hyperresponsiveness among workers in petroleum industry


Objective: To determine the prevalence of respiratory symptoms, lung function test abnormalities and non specific bronchial hyperresponsiveness (BHR) among workers employed in petroleum anaerobic environments.

Methods: A cross sectional study was performed including 45 males (mean age= 41.0±6.8) employed in crude oil refinery (duration of exposure 15±2.6±8) and 40 male office workers as a control group (mean age=46±4.7±5) matched for age, smoking habits and socioeconomic status. Evaluation of examined subjects included completion of a questionnaire on respiratory symptoms in the last 12 months (cough, phlegm, dysnea, wheezing, and chest tightness), spirometry and histamine challenge test (PC20 8±5mg/ml).

Results: Refiner workers had a significantly higher prevalence of cough with phlegm (31.3%), dry-cough (18.9%), wheezing (11.4%), dysnea (4.1%), and non symptoms (8.3%) than the control group (p<0.015). All spirometric parameters (FVC, FEV1, FEV1/FVC6, MEF75-25, MEF50, MEF25) were lower in petroleum refinery workers compared with the control group, but statistical significance was found for MEF25, MEF50, and MEF25 (p<0.02, and p=0.007; respectively). The prevalence of non specific BHR, defined by histamine PC20 less than 8mg/ml, was higher in petroleum refinery workers but statistical significance was still not reached (21.7% vs. 14.7%).

Conclusion: Our study suggest that occupational exposure in the petroleum industry is associated with a higher prevalence of respiratory and nasal symptoms, lung function impairment and higher prevalence of non specific airway responsiveness.

P4185 Dust exposure and respiratory symptoms; cross sectional study in Taiwanese coffee factories

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Introduction: Exposure to coffee dust is associated with respiratory symptoms among workers in secondary coffee processing in industrialized countries, but only three studies have been done in primary coffee factories and none of these studies were in Tanzania.

Aim: This study was carried out to examine whether there is a relationship between total dust exposure and respiratory health effects among workers in Tanzanian primary coffee processing factories.

Methods: A cross sectional study was conducted in two primary coffee factories and in a beverage factory which served as control. Total dust samples were collected throughout the breathing zone from 111 workers in the coffee factory (n = 44) and the control factory (n = 19). Respiratory symptoms were
assessed by standardized ATS questionnaire. Statistical differences were tested by Independent t test and Chi Square. Logistic regression analyses were performed, adjusting for age and smoking.

Results: Totally 150 workers participated; 79 coffee workers and 71 controls. Coffee workers had significantly higher prevalence than the controls for morning cough with sputum (23% vs. 10%, OR = 2.95 [CI 1.1 - 8.4]) and chest tightness (27% vs. 13%, OR = 3.25 [CI 1.2 - 8.7]). Total dust exposure in the coffee factories was significantly higher than in the control factory (geometric mean; 1.23 mg/m³ vs. 0.21 mg/m³, p = 0.001).

Conclusion: Coffee workers in primary factories have higher prevalence for respiratory symptoms and higher dust levels than controls.

P4186
The investigation of stable nitric oxide (NO) metabolites correlation in exhaled breath condensate (EBC) in Cherinolyl clean-up workers (CCUW) with COPD
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The aim of the study was to investigate the correlation between stable NO metabolites in EBC in CCUW with COPD during the course of antioxidant inhalation.

Materials and methods: 58 males outpatients were enrolled in the study. Group1 contains 21 patients CCUW with COPD stage I; group2 contains 19 patients CCUW with COPD stage II. The control group consisted of 18 healthy volunteers. The EBC was collected in all patients, as well as the TNN concentration in EBC was measured before and after the course of therapy. The nebulized ambroxol inhalation (15 mg BID) was carried during 7 days in addition to traditional COPD therapy. The TNN concentration as well as NO3-/NO2- concentrations were measured by spectrophotometric method using the Griess reaction. The correlation between NO3-/NO2-concentration in EBC during the course of antioxidant inhalation was also investigated.

Results: The results obtained demonstrate the statistically significant increase of NO3- concentration and NO2- concentration in EBC in both groups compared with control. The strong positive correlation between observed parameters (r=0.98; p=0.001) as well as linear coefficient k=2.13 (k=[NO3-]/[NO2-]) were determined only in control group. There was a statistically significant correlation between NO3- and NO2- levels in EBC in group1 after the course of ambroxol admission (r=0.89, p=0.003 with k=2.7).

Conclusion: The correlation revealed indicates positive changes in NO metabolites. Thereby, the investigation of NO3-/NO2- correlation in EBC in patients with COPD can be used as a marker of the efficacy of the therapy admitted.

P4187
Biotoxicological pattern and related respiratory impairments in chemical laboratory workers
Felicia Gradinara1, Carmen Crotoru, Brigitte Scutaru, Razvan Danulescu, Micaela Margineanu, Madalina Ipat, Mirela Ghitescu, Eugenia Danulescu. Occupational Medicine Dept, Regional Center of Public Health, Iasi, Romania

Aim: To evaluate the relations between the changes in blood/urine markers and respiratory outcomes in workers from a chemical research institute

Material/Methods: 161 workers (73%women, 27% smokers, having mean age 44.4±13 y) was examined during 20.4±14 yrs) by spirometry, blood/urine biomarkers, including exposure/effect ones. Workplace air solvents level was below upper threshold limits, but noxious cumulative index varied between 1 and 2.

Results: Urinary total phenols releases correlated with TBARS (r=0.22; p<0.05), and urinary acetone with IgM, resp. IgG (r=0.19; p<0.05), showing the relation of the inflammatory effects resp. oxidative imbalance with the occupational hazards. 3/4 of the subjects diagnosed with spirometric changes were in this subgroup, but these changes did not correlate with smoking habit.

Conclusions: Immunological and oxidative stress markers might be related to respiratory changes, even in the early stage of occupational-induced respiratory disease.

P4188
Occupational allergy in apprentices hairdressers and hairdressers in region of Lodz, Poland
Patrycja Krawczyk-Szmul1, Beata Krecisz2, Dorota Chomiczewska2, Marta Wiszniewska1, Marta Kiec-Swierczynska2, Ewa Nowakowska-Swirta1, Joanna Zgorzelska-Kowalik1, Cezary Palczynski 1, Aleksandra Golinska-Zach 1, Jolanta Walusiak-Skorupa1, Patrycja Krawczyk-Szulc1, Beata Krecisz 2, Dorota Chomiczewska 2.

Aim: To specify correlations between UAIS and loss of pulmonary function versus occupational risk, in workers from a small company that processes cotton.

Material and methods: We are investigated 45 workers aged 29-63 years of MW and 77 workers of another trades in meat processing and packing factory, both male and female, mean age 40.1 yrs were examined at the workplace. Respiratory symptoms were recorded on a questionnaire. Lung function tests and peak expiratory flow (PEF) were performed during the shift and out of the work. Blood was collected to determine GSTM1 and GSTT genotypes (PCR).

Results: Airway hyperresponsiveness (AH) and asthma symptoms were recorded in 18 out of 45 (40%) MW after the exposure to PVC fumes, as compared to other workers (19 of 77, 15.6%) p < 0.002. The high prevalence of GSTM1 and GSTT – null genotypes were noticed in 35.5% and 11.8% MW respectively. 7.9% of MW had both deletion of GSTM1 and GSTT. The deletion of the entire genes and absence of the enzymes were associated positively with decreases in FEV1 and PEF (r = 0.67; 0.78) and varied according to the length of service.

Conclusion: Our data suggest that the GSTM1 and GSTT – null genotypes are associated with the higher susceptibility to PVC-induced AH and development of asthma.

P4190
Upper airways irrigation syndrome (U AIS) and loss of pulmonary function at the workers exposed to cotton dust
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Aim: The aim of the study was to assess the prevalence and risk factors of occupational allergy in apprentices hairdressers and hairdressers from the region of Lodz in Poland.

Material and methods: Prospective study was done in apprentices. A group of apprentices hairdressers were tested twice (34 at the beginning of education and 21 at the end) for respiratory and skin allergy. 54 hairdressers were tested for respiratory and 40 for skin allergy.

Results: The prevalence of respiratory symptoms in apprentices after two years at school was not significantly higher after 2 years of education. One student became sensitized to latex. Positive skin prick tests to common allergens was a risk factor of rhinitis related to work in apprentices hairdressers OR= 9.75 (CI 1.03 – 14.64). Prevalence of cough, dyspnoe and rhinitis was significantly higher in hairdressers than apprentices in the 1st class (p<0.05). Smoking was a risk factor of dyspnoe OR=2.17 (95%CI 1.07-5.28) and rhinitis OR=2.44 (95%CI 1.1-5.3) in hairdressers.

Two of 54 hairdressers was sensitized to ammonium persulfate and one to paraphenylenediamine. One subject had an occupational asthma diagnosis.

Contact allergy was common in hairdressers and apprentices, however more prevalent in the first group.

Conclusions:
• Respiratory symptoms were not the most important health problem in apprentices hairdressers at the end of education probably due to “healthy worker effect”.
• Hypersensitivity to common allergens in apprentices and smoking in hairdressers were risk factors of respiratory symptoms.

425. Work, the environment and respiratory disease

P4189
Genetic risk factors for meat wrapper’s asthma
Olga Vasilyeva, Elena Kulemina, Marya Kolyaskina. Occupational Lung Diseases Department, Pulmonology Research Institute, Moskow, Russian Federation

The fumes of polyvinylchloride (PVC) wrap cause respiratory difficulties and meat wrapper’s asthma.

The pathophysiological mechanism for this malady is not clearly understood. Antioxidant enzymes constitute the endogenous defense from toxic products. The M and T classes of glutathione S-transferase play the important role in the response to oxidative stress in the lung.

This study

Aims: To investigate GSTM1 and GSTT- polymorphism in association with bronchial responsiveness and development of asthma in meat wrappers (MW).

Methods: 45 MW and 77 workers of another trades in meat processing and packing factory, both male and female, mean age 40.1 yrs were examined at the workplace. Respiratory symptoms were recorded on a questionnaire. Lung function tests and peak expiratory flow (PEF) were performed during the shift and out of the work. Blood was collected to determine GSTM1 and GSTT genotypes (PCR).

Results: Airway hyperresponsiveness (AH) and asthma symptoms were recorded in 18 out of 45 (40%) MW after the exposure to PVC fumes, as compared to other workers (19 of 77, 15.6%) p < 0.002. The high prevalence of GSTM1 and GSTT – null genotypes were noticed in 35.5% and 11.8% MW respectively. 7.9% of MW had both deletion of GSTM1 and GSTT. The deletion of the entire genes and absence of the enzymes were associated positively with decreases in FEV1 and PEF (r = 0.67; 0.78) and varied according to the length of service.

Conclusion: Our data suggest that the GSTM1 and GSTT – null genotypes are associated with the higher susceptibility to PVC-induced AH and development of asthma.
sneezing (38%) and allergic diseases (18%). The prevalence of the respiratory symptoms was higher among the exposed subjects (p<0.005). The pulmonary function test (PFT) put in evidence a distal obstructive syndrome (DOS) in 20% of the exposed workers (versus 3% at control group; p<0.0002). We found significant increase of obstructive dysfunctions associated with length of service. The mean values of the FEF1.0/FVC ratio and the PEF values are significantly less at the cotton and sugar cane workers (in second part of study) versus the controlled ones.

**Conclusions:** This study reports a high prevalence of UAIS and DOS among workers exposed to cotton dust, which correlated with length of service. It requires technical and organizational measures to reduce occupational exposure to respirable dust.

**P4191 Use of shuttle test on a group of healthy sugar cane workers, Sao Paulo, Brazil**

Monica Barne1, Komalkirti Apte1, Sushmeeta Chhowala2, Basant Pachisia 2, Prevalence of respiratory symptoms in 7154 state road transport workers by our group. Support by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)/Brazil

**Introduction:** The shuttle walking test (ST) is used to assess functional capacity in individuals with pulmonary diseases. Its use in healthy workers may be useful to evaluate exercise capacity. The practice of burning the sugar cane field in the night before harvest is common, and emits large amounts of pollutants.

**Aims:** To evaluate the exercise capacity in a group of the burning sugar cane workers and a control group, during harvest and non-harvesting periods.

**Methods:** 112 sugar cane workers and 107 controls, young man, non-smokers were submitted to ST 2 periods. At the beginning and end of the test, heart rate (HR), respiratory frequency, blood pressure, SpO2 Borg score were measured and the walking distance recorded. Data were analyzed and compared using t-test or Mann-Whitney Test.

**Results:** Mean values of the body mass index (BMI) kg/m² and the HR were higher (p<0.001) in the control group: 29.1±6.4 vs 25.5±2.5 years; BMI: 29.3±6.4 vs 24.6±5.2; HR: (98.4±16.9) vs (84.9±13) bpm, respectively. The median walking distance by the two groups at the end of the test was 1380 (IQI:290) meters. In the period of harvest of sugar cane cutters presented significant increase in (p<0.05) diastolic blood pressure at the end of the exercise. No significant alterations in SpO2 between groups and periods were found.

**Conclusions:** We demonstrated that sugarcane workers (SW) have better physical performance and exercise capacity than control subjects, although SW showed an elevation in diastolic blood pressure in ST, as observed in a previous study by our group. Support by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)/Brazil

**P4192 Prevalence of respiratory symptoms in 7154 state road transport workers from India**

Monica Barne 1, Komalkirti Apte 1, Sushmeeta Chhowala2, Basant Pachisia 2, Monica Barne 1, Komalkirti Apte 1, Sushmeeta Chhowala2, Basant Pachisia 2, Prevalence of respiratory symptoms in 7154 state road transport workers by our group. Support by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)/Brazil

**Methods:** All employees present and willing to participate, from 24 randomly selected bus depots of 7 cities and towns of Andhra Pradesh State Road Transport Corporation (RTC) participated in this cross sectional study. Every individual was administered a respiratory health questionnaire that captured prevalence of respiratory symptoms.

**Results:** 7154 employees (41.4% drivers, 30.4% conductors, 15.9% garage workers, 7.9% office workers) participated in the study. Average age was 41.6±9.9 years. 27% of all the RTC employees had at least one respiratory symptom during the previous 3 months. Prevalences of rhinitis/rhino-sinusitis, cough, wheezing, breathlessness and chest pain/lightness were 14.7%, 10.5%, 8.3%, 7.9% and 5.6% respectively. Prevalence of respiratory symptoms were significantly higher in office workers (34.9%) as compared to drivers (24.2%; p<0.0001), conductors (25.4%; p<0.0001), and garage workers (30.0%; p<0.05). Prevalence of respiratory symptoms amongst garage workers was also significantly higher than drivers and conductors (p<0.0001 and p=0.005 respectively). Smoking was not a confounding factor.

**Conclusion:** Road transport workers have a high prevalence of respiratory symptoms with significantly greater values amongst office based workers and garage workers when compared to drivers and conductors.

**P4193 Evaluation of cardiopulmonary effects and oxidative stress in sugarcane workers compared to a control population exposed to outdoor biomass air pollution**

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Brazil is the world’s largest producer of sugar and alcohol. The practice of burning the sugarcane field in the night before harvesting in order to facilitate cropping and thereby increase productivity is still very common. This biomass burning emits large amounts of particulate (PM) and gaseous pollutants to the atmosphere.

With the aim of studying cardiopulmonary impacts and oxidative stress in a population of 113 sugarcane workers (SW) and 109 local healthy controls (Ci), we evaluated lung function tests (LFTs), blood pressure (BP), heart rate variability (HRV) – in submaximal treadmill protocol – and laboratory tests in pre-harvest and harvest periods. All subjects were male non-smokers. Data were submitted to univariate and LMM multivariate analysis.

**Results:** Median age was 28.4 (C) and 23 (SW); P=0.02. In the harvest period (median atmospheric PM2.5=75.93±g/m³ in sugarcane tillage area vs 27.7±g/m³ in city area) there was a significant higher increase in CPK levels in SW than in control subjects, as well as a higher reduction in LFTs. We also found a significant higher increase in diastolic BP and decrease in HRV among sugarcane workers in harvest period. Another important result, was the statistically significant reduction in antioxidants enzymes SOD, GST and GPX in the harvest period, much more expressive among sugarcane workers than in control subjects. We conclude, therefore, that even in healthy populations, exposure to biomass outdoor pollution can cause cardiopulmonary detrimental effects with potential clinical relevance and that such impacts can be probably explained by the physiopathologic pathway of oxidative stress.

**P4194 Serum biomarkers analysis in workers with occupational salt dust exposure in underground conditions in dependence of length of service**

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**Objective:** We assessed serum biomarkers distribution in underground workers with occupational salt dust exposure in dependence of length of service.

**Methods:** Serum samples of male donors who are not working at Belaruskaliy, and workers employed in underground working conditions of Belaruskaliy with a mean age 46±7 years were enrolled. All donors were divided into 4 groups: Group I included healthy donors who do not work in the enterprise; II - workers with underground work experience of 5 years; III - consisted of workers with underground work experience of 5 to 15 years; IV - workers with underground experience of more than 15 years. To analyze the qualitative composition of serum proteins we obtained by two-dimensional maps of proteins in blood serum from healthy donors and the study group by two-dimensional gel electrophoresis. Proteomic maps were statistically analyzed in dependence of length of service.

**Results:** We found that total protein value in group II-IV differed from the samples of the 1st group. No statistically significant changes have been revealed in the serum protein composition of underground workers. Proteomic maps revealed abnormalities indicating the presence of inflammation in the bronchopulmonary system of workers. This could be the diagnostic indicator of early stages of lung diseases in the absence of clinical evidence.

**Conclusions:** Analysis of serum proteome changes under the influence of sylvinite aerosols could help to search for specific biomarkers of the body functioning of workers under the influence of occupational factors and predict risk of lung morbidity in occupational exposure to sylvinitic aerosols.

**P4195 Occupational risk factors may be of importance to define populations suitable to screening of lung cancer**

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**Aims:** To estimate the attributable fractions (AF) of lung cancer to occupational factors and predict risk of lung morbidity in occupational exposure to sylvinitic aerosols.

**Methods:** A population-based case-control study was performed in the Northern part of Lorraine, France (2006 to 2010). Cases were defined as males with histologically confirmed lung cancer. Controls were selected by a random digit dialing
procedure in the study area. All cases and controls were interviewed in a face-to-face interview in order to fill in standardised questionnaires on risk factors of lung cancer. Occupational exposures were assessed using both a listing of all jobs held for at least one month, specific questionnaires of industrial activities and job-tasks questionnaire. Qualitative and quantitative occupational exposure indices were then calculated. AF and C95% were computed for each occupational exposure index and globally for all significant occupational exposures.

**Results:** 219 cases and 520 controls were included in this study. After adjustment on age, smoking duration, time since quitting smoking, a significant dose-response relationship was found with log of cumulative exposure per unit of air pollution (OR: 1.175, p=0.003), silica (OR: 1.109, p=0.001) and Polycyclic Aromatic Hydrocarbons (OR: 1.175, p=0.007). AF were ranged between 38% (C95%: 27-48) and 57% (C95%: 42-68) according to different models, for these three agents or their association.

**Conclusion:** According to very high AF observed in this study, these results strongly suggest to include occupational risk factors in definition of populations at high risk of lung cancer for the secondary prevention of lung cancer.

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**P4196**

Feather duvet and idiopathic pulmonary fibrosis

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**Introduction:** Up to 5% to 10% of cases of idiopathic pulmonary fibrosis (IPF) may be caused by hypersensitivity pneumonitis (HP) that has been erroneously diagnosed. The hypothesis of this study is that exposure to a feather-filled duvet or pillow can be a cause of pulmonary fibrosis that is erroneously diagnosed as IPF.

**Material and methods:** Between 2004 and 2010, 318 consecutive patients were studied. The diagnosis was based on internationally established criteria. Emphasis was placed on detecting transitory exposure to a possible environmental agent, particularly in the use of a feather duvet or pillow. Furthermore, in patients whose questioning revealed exposure to an uncommon causal antigen or low-intensity exposure, specific IgG to antigen was determined, and specific bronchial challenge (SBC) were carried out. Surgical lung biopsies (SLB) were reviewed.

**Results:** 24 patients had previous contact with a feather duvet or pillow for at least one year. In 15 patients the final diagnosis was HP; 8 by SBC and 2 by characteristic pathologic findings. HP was diagnosed in 3 patients with atypical usual interstitial pneumonia in SLB plus positive IgG testing and 2 patients with bronchoalveolar lavage lymphocytosis (>20%) and positive specific IgG to the causal agent. In 36 patients without previous contact, HP was diagnosed in 8 patients.

**Conclusion:** In IPF, thorough clinical questioning can reveal the existence of a low-intensity, but persistent exposure to a known causal agent. HP due to exposure to a feather duvet can be the cause of some cases of pulmonary fibrosis, a condition that can have different prognosis.

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**P4197**

The value of lymphocytosis in bronchoalveolar lavage in the differential diagnosis between idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis

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**Introduction:** Bronchoalveolar lavage (BAL) is a minimally invasive, well-tolerated bronchoscopy procedure which plays an important role in the diagnosis of interstitial lung disease (ILD). We assessed the value of lymphocytosis in BAL fluid for the differential diagnosis.

**Material and methods:** Prospective study of all the 318 patients with ILD through 2004-2010. During the diagnostic process, cytological and immuno-histochemistry studies of BAL fluid were performed.

**Results:** We studied 318 patients with ILD (57 IPL, 92 NH, 45 Sarcoidosis). BAL was performed in 230 patients (72%), obtaining median lymphocyte percentages of 8%, 20% and 25% in IPF, HP and Sarcoidosis respectively. Lymphocyte counts were >60% in non IPF patients, 5% of HP and in 2% of Sarcoidosis patients; were >30% in non IPF, 18% HP and 29% Sarcoidosis, and >20% in 5% IPF, 32% HP and 33% Sarcoidosis.

In a study focused exclusively on chronic NH occurring with IPF criteria (ATS/ERS criteria) (n=60), three presented lymphocytosis >20% but were ultimately diagnosed with HP. Lymphocytosis >15% was found in 511/45% IPF and 3x3/11 (55%) of patients with final diagnoses HP. Lymphocytosis between 10-15% was present in 8/14 (57%) IPF and 6/14 (43%) HP. No significant differences were found in the cellular profile between IPF and HP.

**Conclusions:** Lymphocytosis >20% is also a characteristic of HP and Sarcoidosis, since it very rarely found in IPF (5% in our series). In chronic HP the absence of lymphocytosis in BAL >20% does not rule out the diagnosis (35% diagnosed with actually HP).

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**P4198**

The relation between air pollution and respiratory tract diseases by months in Duzece City of Turkey

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**Aim:** To investigate the relationship between levels of particulate matter (PM10) and sulphur dioxide (SO2) and the patients with COPD, asthma, respiratory tract infection (respiratory tract disease-RTD) applied to pollicymins in the central part and counties of Duzece.

**Material:** Between I January 2009 and 31 December 2009 in Duzece Atatürk State Hospital, the patients diagnosed as RTD at chest, internal medicine, ENT, pediatric pollicymins were retrospectively evaluated. The monthly average values of SO2 and PM10 obtained from the official data of Ministry of Environment and Forests.

**Results:** 53.1% of 29,367 cases were female. 64.4% of cases were adults. The average SO2 and PM10 concentration was highest in November, December, January and those were the lowest in July, August, September and October. Acute bronchitis were higher than the remaining in January (26.9%) and December (25%), while those were the lowest in September (20.6%), respectively. COPD were more frequent in January (10%), February (10.9%), March (13.1%), but less in September (5.9%). Asthma were most admitted in December (10.6%), January (9.6%) but less frequently in September (6.1%). Pneumonia were frequently admitted in November (10.6%), January (9.6%). The allergic rhinitis was the most common at the seaside (119/479, 24.8%) (p=0.000). Upper RTD (58%) were higher than the lower RTD in the months that the air pollution was the highest (p=0.000).

**Conclusion:** It was speculated that pollicymins admissions of COPD, asthma, acute bronchitis, pneumonia seem to be associated with air pollution and also living in the seaside may lead to more increase in applications regarding allergic rhinitis.

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**P4199**

Influence of high values of air pollutants on number of asthma exacerbations in children from Pancevo in years 2009 and 2010

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**Introduction:** Air pollution is well known for its influence on development of asthma. Children with asthma are specially vulnerable on high levels of air pollutants.

**Aim:** To show that elevated air pollution (tar, SO2, NO2, TSP, NH3, and benzene) had significant influence on acute exacerbations of asthma.

**Method and results:** We have monitored daily concentrations of tar, SO2, NO2, TSP, NH3, and benzene in city of Pancevo in October, November, December, January and February and number of children who visited pediatrician due to acute asthma exacerbation. We have excluded other months to avoid influence of higher levels of pollen. We have observed that during periods with high peaks of tar, TSP and benzene, larger number of children had acute asthma exacerbation and visited pediatrician. SO2, NO2 and NH3, were within legally permitted range.

Results have shown that in year 2009 in January, February, November, October and December tar, TSP and benzene were above permitted values 73 days and in that period 1763 children had asthma exacerbation. In the same period in 2010 the same air pollutants were 44 days above permitted values and 939 children had asthma exacerbation. During periods with air pollution below permitted values in 2009, 1331 children had asthma exacerbation in 78 days, and in 2010, 1508 in 107 days. This difference is statistically significant, which was confirmed by χ2 test, for year 2009 χ2 = 3.987, and for 2010 χ2 was 4.91, p>0.05.

**Conclusion:** High concentrations of tar, TSP and Benzene have significant influence on larger number of asthma exacerbations in children, specially during periods of overstepping legally permitted concentrations.

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**P4200**

The relationship of air pollution and surrogate markers of endothelial dysfunction in a population-based sample of children

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**Background:** This study aimed to assess the relationship of air pollution and plasma surrogate markers of endothelial dysfunction in the pediatric age group.

**Method:** This cross-sectional study was conducted in 2009-2010 among 125 participants aged 10-18 years. They were randomly selected from different areas of Isfahan city, the second largest and air-polluted city in Iran. The association of air pollutants’ levels with serum thrombomodulin (TM) and tissue factor (TF) was determined after adjustment for age, gender, anthropometric measures, dietary and physical activity habits.
Tuesday, September 27th 2011

Results: Data of 118 participants was complete and was analyzed. The mean age was 12.79 (2.35) years. The mean pollution standards index (PSI) value was at moderate level, the mean particular matter measuring up to 10 mum (PM10) was more than twice the normal level. Multiple linear regression analysis showed that TF had significant relationship with all air pollutants except carbon monoxide, and TM had significant inverse relationship with ozone. The odds ratio of elevated TF was 5.16 higher in the upper vs. the lower quintiles of PM10, ozone and PSI. The corresponding figures were in opposite direction for TM.

Conclusions: The relationship of air pollutants with endothelial dysfunction and pro-coagulant state can be an important factor in the development of alterations in microcirculation from early life. This finding should be confirmed in future longitudinal studies. Concerns about the harmful effects of air pollution on children’s health should be considered a top priority for public health policy; it should be underscored in primordial and primary prevention of chronic diseases.

P4201 Prediction of the acute mountain sickness using SaO2 indices at rest and exercise in hypoxic conditions

Akpay Sarybaev, Almaz Akunov.

The aim of the study was to compare the oxygen saturation at rest and exercise during the simulated altitude ascents in subjects who had suffered from acute mountain sickness (AMS) as well as healthy subjects. Ninety seven subjects were divided into three groups depending on the Lake Louise score during the previous stay at high altitude (3800 m above sea level). The 1st, control, group consisted of 62 people without AMS symptoms; the 2nd group included 18 patients with mild AMS (3-4 points in LL score) and 17 subjects with moderate to severe AMS made the 3rd group (5 or more points in LL score). SaO2 indices were taken at rest and after 5 minutes of strenuous bicycle test both at normoxia (760 mm) and inside the hypobaric chamber (4500 m above sea level, 30 minutes).

Results: It was revealed that rest oxygen desaturation rate was significantly higher in the 2nd and 3rd group compared with the 1st, control, group (rest SaO2 – 16.0±0.5% and 16.5±7% compared with 14.2%, p<0.05) while the exercise oxygen desaturation rate was significantly higher in the 3rd group compared with 1st and 2nd group exercise SaO2 – 24.7±0.8% compared with 18.5±4.8% and 21.7%, p<0.05).

Conclusion: Both rest and exercise indices of oxygen saturation during the simulated ascent to high altitude may be used as prediction markers for acute mountain sickness.

P4202 Airborne particulate matter (PM10) decreases respiratory activity in mitochondria isolated from lung tissue

Norma Elena De la Fuente-Hernández1, Verónica Freyre-Fonseca1, Claudia María García-Cuéllar1, Yesenia Sánchez-Pérez2, Yolanda I. Chirino2.

Airborne particulate matter (PM10) has potential adverse health effects in human, especially in lung tissue and those effects are related to an increase in several dis ease and cancer. We have previously demonstrated that PM10 increases reactive oxygen species (ROS) formation, decrease in antioxidant enzymes activity and these effects are observed under sub-lethal conditions. In this regard, mitochondrion are the main source of ROS but little is known about alterations induced in mito- chondrial function after PM10 exposure. We hypothesized that if PM10 induces an increase in ROS generation, it could be possible to find alterations mitochondrial function. To test our hypothesis we exposed enriched mitochondria preparations from lung tissue of rat for 1 hour to the following PM10 concentrations: 1, 5, 10, 30 and 50 μg/mL. We measured the oxygen consumption after PM10 exposure using a Clark type electrode and also the activity of mitochondrial complexes. In addition, the mitochondrial membrane potential was determined by rhodamine 123 staining using confocal microscopy. Our results showed a decrease in the respiratory control index and ADP phosphorylation over 50%, a decrease in the respiratory activity of complex IV and an important decrease in mitochondrial membrane potential. In conclusion, PM10 induces a decrease in oxygen consumption, ADP phosphorylation and loss of mitochondrial membrane potential. These effects are related to the decrease in activity of complex IV. Our research will be guided to investigate if the mitochondrial alterations induced by PM10 exposure could be related to mitochondrial dysfunction and metabolic alterations found in cancer cells.

P4203 Prevalence of asthma and allergy symptoms and pulmonary function testing in sugar cane and tobacco field workers in Honduras

Johan F. Salas, Maria E. Perez, Indiana University School of Medicine, Indianapolis, IN, United States

We previously demonstrated a very high prevalence of wheezing (89%) and lower pulmonary function tests (PPT) in rural Honduran children of the Rio Grande O Choluteca valley where sugar cane is burned 8 months of the year compared to children of Jamastran valley (17% wheezing) where no crops are burned. We applied a similar asthma/allergy questionnaire and performed PPT on sugar cane field workers (SC) of the Rio Grande O Choluteca valley and tobacco field workers (TOB) of the Jamastran valley. Tables 1 & 2 summarize questionnaire findings and PFT values of the two groups.

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<th>Table 1. Questionnaire findings</th>
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We found the SC workers to be significantly younger with thus fewer years working in the fields compared to the TOB workers. Both groups were found to have similarly high prevalence’s of ever wheezed, wheezed in last 12 months, night cough, smoking frequency, chronic rhinitis and conjunctivitis. SC workers have significantly lower FVC and FEV1-1. We conclude that both SC and TOB field workers in Honduras have a high prevalence of asthma and allergy symptoms and SC workers, although younger with fewer years of exposure, have lower pulmonary function. Individual air quality sampling of the two groups is needed to delineate the contribution of environmental work exposure to these findings.

P4204 Asthma and allergy to laboratory animals in university employees: Need for prophylaxis

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Introduction: Subjects exposed to laboratory animals are at high risk of developing respiratory and allergic diseases. The reported prevalence of occupational asthma ranges from 1.4 to 9.5%, and occupational rhinitis from 2.9 to 18.3% (reviewed by Foletti, L. et al. Allergy 2008; 63:834-41). In the moment, few studies have looked at programs to prevent these diseases.

Objectives: To assess the prevalence of asthma and atopic sensitization to common allergens, and to evaluate the employment of prophylactic measures in two Brazilian universities.

Methods: Subjects exposed to laboratory animals in two Brazilian universities (University of São Paulo and State University of Campinas) answered specific questionnaires to assess work conditions, underwent spirometry, bronchial provocation with mannitol, and skin prick tests to eleven common allergens and five work-related allergens (rat, mouse, guinea pig, hamster and rabbit).

Results: Eighty-five subjects (38/11 years old, 59 men) were evaluated. Forty-four (51.8%) subjects were sensitized to at least 1 common allergen, and nine (10.6%) were sensitized to at least 1 work-related allergen. Twelve subjects (14.6%) presented hyperresponsiveness to mannitol. Personal protective equipments were available at work for 98%; however, 51% did not wear mask all the time when in contact with animals. Twenty-six percent of subjects received formal orientation about the risk assessment and hazard recognition related to laboratory animal allergy.

Conclusion: In this ongoing study, prevalence was relevant to support prophylactic measures. These measures need reinforcement.

P4205 COPD and exposure to smoke biomass in non-smokers women in a semi-rural region of Tunisia

Nada Rahmouni, Ines Zendah, Bithel Khouaja, Leila Bayahi, Amel Khattab, Habib Ghedira. Pulmonary Department I, Abderrahmen Mami Hospital, Ariana, Tunisia

Many studies have suggested that biomass smoke is a risk factor for COPD and this study is conducted to compare, in non-smokers housewives, the prevalence of COPD symptoms and airway obstruction as related to biomass exposure.

Methods: From April to October 2010, 243 women over 30 years-old were ran- domly selected from a municipal list of the semi-rural city of Kasserine in Tunisia. Among the 140 non-smokers women who consent to be explored, 81 (58%) are exposed to smoke biomass from traditional wood cooking (n=47) or traditional field workers in Honduras have a high prevalence of asthma and allergy symptoms and SC workers, although younger with fewer years of exposure, have lower pulmonary function. Individual air quality sampling of the two groups is needed to delineate the contribution of environmental work exposure to these findings.

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PFT values of the two groups.

We have looked at programs to prevent these diseases.

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Table 2. PFT % predicted (mean ± 1SD).
related symptoms were more frequent in exposed women either Cough (81% vs. 66%, p<0.01) or Dyspnea (76% vs. 24%; p<0.01). An FEV1/FEV6 of less than 70%, considered as diagnostic of an obstructive disease, was more prevalent in exposed group (23.3% vs. 4.4%; p<0.001).

Conclusion: COPD-related symptoms and airway obstruction are significantly more prevalent in non smokers women, from semi rural area in Tunisia, exposed to biomass smoke from traditional wood cooking or traditional coal house heating.

P4206 Smoking and obstructive sleep apnea among former World Trade Center (WTC) rescue workers and volunteers

Background: Smoking and sleep disorders are common among individuals with adverse health effects from their WTC work exposures. Previous observations seemed to suggest that some forms of sleep disordered breathing (SDB) could be more prevalent in this population. We reviewed the results from nocturnal polysomnograms (PSG), to investigate whether REM-related OSA, and upper airway resistance syndrome (UARS) were more frequently diagnosed among WTC-exposed subjects compared to unexposed subjects.

Methods: 656 nocturnal PSGs performed at our sleep center were reviewed, 272 of them in former WTC workers. The diagnoses were categorized as: no SDB, simple snoring, REM-related OSA, UARS, and mild, moderate, and severe OSA. Bivariate and logistic regression analyses were used to examine differences in diagnoses between the two groups, using age, gender, body mass index (BMI) as predictors.

Results: The WTC group had a significantly higher predominance of the male gender (86.8% vs. 56.3%, p<0.001), but slightly lower mean BMI (31.4 vs. 33.2 kg/m2, p=0.002). Table 1 summarizes the diagnoses on PSG. There was no significant difference between the two groups by Chi square (p=0.56), or logistic regression (p=0.77) with adjustment for the 3 significant predictors (age, gender, and BMI, all p<0.0001).

Conclusions: We did not detect any difference in the diagnoses derived from PSG between the WTC-exposed and unexposed subjects. OSA was significantly associated with age, BMI, and gender in this patient population.

P4207 Black carbon content in PM as a metric to evaluate the impact of the car-free Sundays of winter 2011 on air quality in Milan

Methods: The overall prevalence of COPD was 7.5%, the odds ratio (OR) of occupational exposure was 4.6 (95%CI 1.9-10.9), the prevalence of smoking was 17.5% (95%CI 14.5-20.7). Results of the statistical analyses showed that the contribution of occupational factors in the development of COPD was 18.3% (95%CI 13.8-23.6). The contribution of smoking was 55.8% (95%CI 49.5-62.4). The contribution of age, gender and BMI was 26.9% (95%CI 20.6-33.6).

Conclusions: COPD-related symptoms were more frequent in non smokers women, from semi rural area in Tunisia, exposed to biomass smoke from traditional wood cooking or traditional coal house heating.

P4208 The influence of occupational and non-occupational factors on the development of occupational COPD

Methods: By the 13th of February 2011 the number of days exceeding 50 gg/m3 of PM10 was over the EU annual limit of 35. The Milan Municipality decided to stop traffic 8 am to 6 pm on Sunday Jan 30th and Feb 6th 2011 to reduce pollution. The decision was opposed by detractors, who claimed that no data were available about the efficacy of the restriction.

Scope: To measure outdoor PM10, PM2.5, PM10, and black carbon (BC) during car free Sunday and normal traffic days, and to compare air quality as the percent content of BC in PM (BC/PM).

Methods: Instrumentation: mass analyzer mod. Aerocet 531 (MetOne, USA) for PM concentrations, Microaethalometer mod. AE51 (Magee, USA) for BC. Procedure: the instruments were located at walkside in Corso Buenos Aires and were tested by 04:00 to 07:00 p.m. from Friday to Monday. Traffic density was also recorded.

Results: Overall the BC/PM mean (SD) was 5.8 (2.3) during the car free Sundays as compared to 12.04 (4.8) during the free traffic days (p<0.001).

Table 1. Percent black carbon content in PM during car-free Sundays vs normal traffic days

<table>
<thead>
<tr>
<th>Car-free Sunday Jan 30th and Feb 06th 2011</th>
<th>Normal traffic from Friday, Saturday and Monday</th>
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<tr>
<td>%</td>
<td>BC/PM ratio mean (SD)</td>
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<tr>
<td>%</td>
<td>5.80 (2.3) *</td>
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</table>

*p<0.01 Student’s t-test

Mean traffic density was 342 and 1858 vehicles/h during the car-free and normal traffic days, respectively.

Conclusion: During the 2 car-free Sundays, a great improvement in air quality was observed, with over 50% reduction in BC/PM ratio. These data show that car free Sundays represent a useful environmental intervention to protect people from traffic proximity pollution, a well known respiratory and CV risk factor.

P4209 Breast change perception in women after smoking cessation

Methods: We interviewed 25 premenopausal women who had quit smoking quitting. Such an outcome was paralleled by only moderate effects on weight or BMI increase after quitting: Notably, of the 16 women with breast change perception, only 3 (19%) with a normal baseline BMI showed a BMI increase to >25.

Conclusions: These results indicate that women in pre-menopausal status reported subjective perception of change in breast size after smoking cessation, which may not be totally explained by weight gain. Further studies are needed to understand the effect, if any, of such perception on motivation to quit smoking.

426. Anti-smoking interventions: prevention and treatment

P4209 Breast change perception in women after smoking cessation

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P4210 Smoking prevalence and its effect on lung function and soluble adhesion molecules levels in medical students
Ekaterina Kukhareva1, Nikolay Menkov1, Natalia Lubavina1, Monica Shonia1, Galina Varvarina1, Victor Novikov1, 2, 3 Propedeutics of Internal Medicine, Medical State Academy, Nizhny Novgorod, Russian Federation; 4 Cell and Molecular Biology, Lobachevsky State University, Nizhny Novgorod, Russian Federation

The purpose of the study was to investigate the prevalence of tobacco smoking in students of Nizhny Novgorod Medical State Academy (Russia) and its effects on lung function and serum levels of soluble intercellular adhesion molecules (sICAM-1, sCD50, sCD54) and sCD54 (sICAM-3). Materials and methods: Data were collected between 2009-2010 using a structured questionnaire on 149 medical students (42 males and 107 females), aged 20±1 years. The questionnaire included questions regarding personal characteristics, history and quitting smoking, consequences on health. Lung function tests were performed in 31 students (16 smokers and 15 non-smokers). The serum concentrations of sICAM-1 and -3 were determined using ELISA method.

Results: In 40% of current smokers (from which 46% females); an index of duration of smoking was 3,0±1,9 pack/years. The early age of the beginning of smoking (of 9-14 years) has been registered. Means of FVC and PEF in smoking students were significantly lower than in non-smoking (81,1±6,5 vs 87,3±4,91%, and 75,4±9,7 vs 84,9±7,66, respectively). The serum levels of sCD50 and sCD54 in smoker (140,4±57,7 L/ U and 78,9±29,7 U/L, respectively) were significantly reduced compared with non-smoker (242,4±54,4 U/L and 172,7±51,5 U/L, respectively). Conclusion: These results indicate high level of tobacco use among medical students in this Russian city, especially among females. The reduced levels of FVC and PEF in all of sCD54 and -3 in smoker compared with non-smoker were revealed. Decrease in levels of sCD50 and sCD54 in smokers might be due to inhibitory effect of smoking on intercellular adhesion.

P4211 The role of smoking in development of endothelial dysfunction in patients with COPD: combination with AH
Oxana Belina1, Natalia Shapovalova1, Maria Menshutina2, Vera Achkasova3, Olga Galkina1, Margarita Kadyskaya1, Vera Didur1. General Practice Department, Pirogov’s State Medical University, Saint-Petersburg, Russia; 2 Pathophysiology Department, Saint-Petersburg Pirogov’s State Medical University, Saint-Petersburg, Saint Petersburg, Russian Federation; 3Department of Laboratory Diagnostics, Saint-Petersburg Pirogov’s State Medical University, Saint-Petersburg, Russian Federation

Endothelial dysfunction (ED) is a pathological finding of COPD and arterial hypertension (AH) at different stages of incidence of AH in patients with COPD is higher than in the population. The important risk factor of COPD and AH is smoking which may initiate vascular impairment by stimulate adhesion molecule expression and leukocyte adhesion to endothelium.

Aims: The purpose of study was to find out the role of ED in the pathogenesis of COPD in combination with AH using sICAM-1, and to study the reversibility of changes in the endothelium after smoking cessation.

Methods: Plasma levels of sICAM-1 were quantified by ELISA in age-matched 45 patients with COPD and AH (mean age 61±6,5) that were either current smoking COPD patients with AH (n=12) and COPD ex-smokers with AH (n=12), to be compared with smokers (n=10) and nonsmokers with AH (n=11).

Results: The comparison of smoking (19,5±4,8) and ex-smoking (15,5±3,6) COPD patients with AH revealed that level of sICAM-1 was higher in smokers (p<0.05). There is no difference in smokers with AH (14,7±4,5) comparing with non-smokers (16,5±4,7). We have found difference between smokers with COPD and AH and smokers with AH (p<0.05), and a correlation between sICAM-1 plasma level and the age (r=0.46,p<0.05).

Conclusions: Our results show that COPD smokers with AH have more evident expression of adhesion molecule to endothelium to be compared with ex-smokers. The combination of COPD and AH may have more evident contribution in development of ED. The less evident of ED in ex-smoking patients shows reversibility of these changes. Correlation between sICAM-1 and age shows that ED in elderly patients plays important pathogenetic role in comparing with middle age patients.

P4212 Acute effects of water-pipe smoking on pulmonary function and cardio-pulmonary exercise capacity in healthy subjects
Feras Hawai1,2,3, Hiba Ayub1, Nour Obiedat1, Iyad Ghanimat2, Sahar Dawaalrah1, Thomas Eissenberg3. 1 Cancer Control Office, King Hussein Cancer Center, Amman, Jordan; 2 Department of Laboratory Diagnostics, Saint-Petersburg Pirogov’s State Medical University, Saint-Petersburg, Russia; 3Psychology and Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, United States

Background: Waterpipe tobacco smoking (WTS) has gained popularity, but the physiologic effects of WTS have not been extensively studied. Studies that have evaluated the impact of WTS have focused on its chronic effects or have only evaluated limited parameters. In a pilot study, we evaluated the acute effects of WTS on lung function and exercise capacity in water-pipe users. We hypothesized that acute exposure to WTS alters pulmonary function and cardio-pulmonary exercise test (CPET) responses.

Methods: We recruited 15 healthy WTS male subjects (8). We used a single-group pre-test (having abstained from WTS for at least 48 hours before testing) post-test (within half an hour of 45-minute WTS session in a café design). We performed spirometry and CPET (cyclogrometer; 2-min 20-Watt warm-up and 25-Watt increase every 2-min for 10 min).

Results: Mean age was 21.2 years; average carbon monoxide pre-test was 4.6 ppm and 27.5 ppm post-test; forced expiratory volume in one second (FEV1) decreased in 7/15 S by 0.48 L/sec (9%), forced expiratory flow from 25% to 75% of vital capacity (FEF25-75%) decreased in 11/15 S by 0.65 L/sec (12%). Breathing reserve decreased in 10/15 S by 10.2%; oxygen pulse decreased in 9/15 S by 2.4 mL/beat (8%). 9/15 S could not complete the CPET after WTS (8.29 min average), vs. 6/15 S pre-WTS (8.33 min average); 9/15 S reported greater degree of shortness of breath at mid/peak exercise using Borg scale; among those completing exercise time pre and post (6/15 S), maximum oxygen consumption (VO2max) dropped in 9/15 S.

Conclusion: Acute WTS causes impairment in pulmonary function and CPET ventilatory and cardiovascular responses.

P4213 Waterpipe smoking in Lebanese women: A lower prevalence but a higher risk of dependence
Pascale Salamé1, Georges Khayat2, Mirna Waked3. 1 Faculties of Public Health & of Pharmacy, Lebanese University, Beirut, Lebanon; 2Pulmonology, Hotel Dieu de France Hospital, Beirut, Lebanon; 3Pulmonology, Saint George Hospital, Beirut, Lebanon

Introduction: Waterpipe smoking has gained in popularity among Lebanese women. Our objective was to evaluate whether nicotine dependence is higher in smoking women compared with men.

Methods: Data were taken from a cross-sectional study on Lebanese residents aged 40 years and above. After an oral informed consent, subjects answered a questionnaire, including smoking history, cigarette and waterpipe dependence using validated dependence questionnaires (Fagerström for cigarettes and LWDSS-11 waterpipe). Results: 1066 males and 1134 females were interviewed; respectively, 58.7% and 42.9% of them had ever smoked cigarettes, while 6.9% versus 6.7% had ever smoked waterpipe (p<0.01). Similar results were found for actual and previous smokers. However, when looking at dependence, patterns differed between genders: 57.5% vs 49.1% in cigarette smokers (p=0.041), 35.9% vs 51.6% in waterpipe smokers (p=0.076), and 67.9% vs 43.6% in mixed smokers. These results were confirmed by dependence dose-effect relationship (p=0.05 for trend) and multivariate analysis (ORa=2.28). The main components of waterpipe dependence in women were positive and negative reinforcement (p<0.05), but not nicotine dependence or psychological craving. In female waterpipe smokers, a higher prevalence of respiratory disease and symptoms were found.

Discussion and conclusion: Since tobacco dependence seems highly associated with tobacco related diseases, waterpipe smoking women could be at a higher risk of disease; they should be considered as real smokers, and receive particular attention during tobacco related health education and in smoking cessation treatments.

P4214 Smoking in posttuberculosis bronchiectasis syndrome patients
Beatrice Mahler. Pneumology, “Marius Nasta” Institute of Pneumology, Bucharest, Romania

Bronchiectasis is the permanent dilation of the bronchial airway. Posttuberculosis bronchiectasis syndrome occurs with the healing of extensive and destructive tuberculosis. The frequency of this association is 15-20%. The smoking – active bronchiectasis syndrome occurs with the healing of extensive and destructive tuberculosis. The frequency of this association is 15-20%. The smoking – active tuberculosis sequelae, mean age of 48.4 (± 16.6). We compared the share of smokers in the two categories.

Results: In the group of idiopathic bronchiectasis patients, the fraction of smokers was 60.52%, with a 32.1% of the group. In the group of patients with bronchiectasis secondary to tuberculosis, the fraction of smokers was 71.42%, with a 30.2% of the group.

Conclusions: The number of smokers among posttuberculosis bronchiectasis patients was higher, although the PA index was lower in idiopathic bronchiectasis patients. The high smoking rate in patients with idiopathic bronchiectasis, as well as the PA index was surprising. I believe the high smoking rate in patients suffering from the posttuberculosis bronchiectasis syndrome was due to their poor socio-economic conditions, which also explains a lower PA index, as well as to the need of implementing health education programs for these categories.
P4215 Interrelationship between clinical picture expressiveness and brush-biopsy cell count and proteinases and its inhibitors in sputum at smokers and nonsmokers with COPD
Ekaterina Bukreeva1, Raisa Pleshko2, Gulnara Seitoval2. 1Therapy, Siberian State Medical University, Tomsk, Russian Federation; 2 Morphology, Siberian State Medical University, Tomsk, Russian Federation
We study relationship between clinical picture and expressiveness of changes in bronchi at COPD smokers and nonsmokers. Endobronchial biopsy and brush-biopsy cytological research and definition of elastase and its inhibitors in sputum were conducted at 46 COPD patients. To reveal correlations we used Spearman coefficient. At COPD nonsmokers the expressiveness of cough and dyspnoe has positive correlation with neutrophiles count (R=0.95), dystrophical epithelial cell count (R=0.95) and negative correlation with eosinophiles count (R=-0.95). COPD nonsmokers have positive correlation between elastase activity and goblet cell count (R=0.81) and atrophical epithelial ciliated cell count (R=0.83). It is evidence of influence of elastase on development of atrophy and hyperscretion in COPD exacerbation program. COPD smokers have no correlation between cough expressiveness and brush-biopsy cell count, but dyspnoe expressiveness has positive correlation with neutrophiles count (R=0.42), and negative with lymphocytes count (R=-0.70). At COPD smokers the negative correlation was revealed between FEV1, and dystrophical epithelial cell count (R=-0.40), between a2MG and reserved cell count (R=0.42), positive correlation between a2MG and typical epithelial ciliated cell count (R=0.46), proliferated epithelial ciliated cell (R=0.56). That may be caused by capacity of a2MG to increase count of cell mitoses. Smoking influences on inflammation mechanisms at COPD patients, that is reflected on correlations between brush-biopsy cell count, proteins and its inhibitors in sputum and clinical symptoms expressiveness.

P4216 Determinants of change in quality of life after smoking cessation of health care employees
Rebecca Finger1, Michael Tammi1, Bruno Seiffert1, Martin Kuster2, Anja Meyer1, Daiana Stolz1. 1Clinical of Pulmonary Medicine and Respiratory Cell Research, University Hospital of Basel, Basel, Switzerland; 2Industrial Health Service, Novartis Pharma AG, Basel, Switzerland
We aimed to assess the influence of a smoking cessation programme on quality of life (QoL). 703 smoking employees from University Hospital Basel, Switzerland, and two local health industry companies (Novartis Pharma AG, Hoffman-La Roche AG) participated on a structured smoking cessation program. This consisted of 10 visits with counselling and motivational within 2 years of follow-up. Various modalities of nicotine replacement therapy and/or bupropion were offered. Quality of life was assessed by Satisfaction with Life scale (QoL). The impact of several factors on quality of life was analyzed by linear mixed effect model (fixed effects with 95% confidence intervals are shown in parentheses).

38% of participants were abstinent from nicotine after 2 years. Successful quitting at 2 years was associated with a significant improvement in quality of life (0.75 95% CI 0.0151;49; p=0.045). Smokers with higher quality of life (QoL) at baseline showed greater improvement than those with lower baseline values (0.5 95% CI 0.42;57; p=0.001). Changes in quality of life were affected by medication after a successful quit attempt (p=0.029) and the interaction of time and medication (p 0.02).

P4217 Public spirometry for primary prevention of smoking-related diseases?
Christina Wich1, Sabine Zirlik1, Markus Frieser1, Kai Hildner1, Markus Neurath1, Christina Wich1, Sabine Zirlik1, Markus Frieser1, Kai Hildner1, Markus Neurath1, Masatada Soejima1, Hiroyuki Nagahama1, Hirotsugu Tsunobuchi2. 1Division of Pulmonary Medicine, Respiratory and Stress Care Center, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan; 2Department of Digestive and Life-Style Related Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan
Background: Several reports showed the IPAG-Questionnaire (Q) is useful for screening COPD, but may require modification for Japanese. However its modification hasn’t been reported yet.

Objective: The aim of this study was to establish a modified IPAG-Q for Japanese. Method: Smokers (excluding those with a history of bronchial asthma) aged 40 and over who underwent a screening CT and had given written informed consent were enrolled. They were classified into two groups based on the results of respiratory function tests (FEV1% < or ≥ 70%): control-smokers and a COPD group. We compared the original IPAG-Q between the two groups and statistically analyzed the results to modify it.

Results: A total of 268 subjects (control-smokers/COPD: 244/24) were enrolled. We described the receiver operating characteristic (ROC) curve about the original IPAG-Q: the area under the ROC curve (AUC) was 0.764, cut-off was 18.5±50.5 (score), sensitivity was 0.750 and specificity was 0.615. Logistic regression analysis revealed only “sneeze frequency” was useful in the “symptoms/history”, so we deleted “symptom/history” except for this parameter. And we improved the stratification for age, BMI, and pack/year: age ≥ or < 50 yrs. BMI <18.5 or ≥ 18.5 & < 25.0 or ≥ 25.0, and pack/year ≥ or < 30. We then constructed a new scoring system based on the original model and validated it on a modified IPAG-Q for Japanese. This modified model was proved valid in the ROC curve; AUC was 0.828, cut-off was 8.5±50.5 (score), sensitivity was 0.833 and specificity was 0.672. This model was superior to the original one.

Conclusion: Our modified IPAG-Q is of greater use for screening COPD among Japanese than the original one.
Motives to quit smoking: Insight from the Melen study

Leyla Yılmaz Aydın,1 Hakon Ozhan2, Talha Dumlul3, Saber Dikici1, Melih Engin Erkan1, Suha Bulur4, Adem Gungor5, Gökhan Celbek5. 1Chest Diseases, Duzce University, Medical Faculty, Duzce, Turkey; 2Cardiology, Duzce University, Medical Faculty, Duzce, Turkey; 3Neurology, Duzce University, Medical Faculty, Duzce, Turkey; 4Nuclear Medicine, Duzce University, Medical Faculty, Duzce, Turkey; 5Internal Medicine, Duzce University, Medical Faculty, Duzce, Turkey

Background: Ethnic, cultural and social factors influence the motives to quit smoking.

Aim: To investigate the current prevalence of smoking and motives to quit on smoking cessation in Turkey in a large population-based epidemiologic study.

Methods: A total of 2298 subjects with a mean age of 50 (age range 18 to 92) were interviewed. The subjects reported information regarding socio-economic status, medical history and current use of medications. Tobacco use behaviors (current status of smoking, number of cigarettes smoked daily, duration of smoking, age of addiction, attempts and desire to quit) and motives of quitting were asked.

Results: Sixty five percent of the study population (1495 subjects) had never smoked. Three hundred eighty nine subjects were current smokers where as 414 subjects had quit smoking. Crude smoking rate of the population was 17%. The most frequent motive was the smokers' health status (having a chronic disease that urged the patient to use drugs daily and continuously). The most common motive in primary prevention was the assistance of a physician. Self motivation and religious beliefs showed better success rates. Age and existence of chronic diseases were found to be the independent predictors of quitting (Odds ratio (OR): 1.37-3.18, p: 0.007).

Conclusions: Prevalence of smoking is decreasing in Turkey. Smoking ban, cost, physician assistance, comorbidities, notices on packages, religion, care for family members and self motivation are the most important motives to quit.

Factors associated with different patterns of adherence to treatment in a smoking cessation unit

Carlos Almonacid Sanchez, Jose Gallardo Carrasco, Ignacio Sanchez Hernandez, Juan Pablo Rodriguez Gallego, Elisabeth Guzman Robles, Jorge Castelo Naval, Jesus Fernandez Frances, Saray Quiros Fernandez, Jose Luis Izquierdo Alonso, Pilar Rosano Barro, Olga Mediano. Palomar Medicine, Hospital Universitario de Guadalajara, Guadalajara, Spain

Objective: Identify different patterns of adherence to therapy in the treatment of patients attending a specialized smoking cessation unit.

Material and methods: Retrospective cross-sectional study of a sample of smokers who come for smoking cessation. The sample was divided into 4 groups: group 1, who only attend the first visit, group 2, persons who do not attend all visits and not answering phone calls, group 3, people who do not attend all visits but answer phone calls to complete a period of 6 months of treatment, group 4, all patients attending follow-up visits. The collection period runs from January 2004 to June 2010. Data were collected at each visit following the same methodology using an electronic medical record designed for this purpose.

Results: We analyzed a total of 1545 people who attended the clinic. The results are summarized in Table 1. The quantitative variables are described as mean and standard deviation. The qualitative variables are described as total and percentage.

Conclusions: Age, a lower level of motivation, the coexistence of psychiatric disorders and increased consumption of cigarettes are associated with poorer adherence to treatment.

Smoking cessation ward rounds – The impact on smoking patterns

Jessica Maycock, Victoria Foy, Patrick Mulholland, Dilip Nazareth, Simon Twite, Paul Stockton. Respiratory Department, St Helens and Knowsley Teaching Hospitals NHS Trust, Liverpool, United Kingdom

Background: Smoking cessation is a NHS (UK) priority and all health care professionals are encouraged to refer smokers to a “stop smoking” service. Many UK public health campaigns have targeted smokers. Our busy District General Teaching Hospital introduced a daily “targeted” smoking cessation ward round in 2008. This study evaluates the impact of this, on smoking patterns.

Results: 136 patients were surveyed in 2008 and 187 in 2010. 58% of both groups had a history of smoking. 69% were current smokers in 2010 and 35% in 2008. Of the smokers, 73% in 2008 had tried to quit compared to 68% in 2010. The percentage of smokers offered educational material while in hospital increased from 29% in 2008 to 38% in 2010

The table below summarises reasons for patients deciding to quit smoking:

Table 1: Reasons for smokers deciding to quit

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<thead>
<tr>
<th>% 2008 (n=58)</th>
<th>% 2010 (n=77)</th>
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<tbody>
<tr>
<td>Personal illness</td>
<td>19</td>
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<tr>
<td>Social pressure</td>
<td>39</td>
</tr>
<tr>
<td>Medical advice</td>
<td>12</td>
</tr>
<tr>
<td>Cost</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusions: There has been a marked increase in the number of patients deciding to quit smoking following education and advice from medical professional’s. The number of smokers who decide to quit due to personal illness has also increased. A new daily smoking cessation ward round and additional support from healthcare professionals is considered to have significantly increased the uptake of smoking cessation advice in this group of patients.

Effectiveness of a cognitive orientation program with and without nicotine replacement therapy in stopping smoking in hospitalised patients

Borja Valencia, Francisco Ortega, Arturo Vellisco, Eduardo Márquez-Martín, Jose Luis López Campos, Ana María Rodríguez, Marta Ferrer, Pilar Cejudo, Borja Valencia, Francisco Ortega, Arturo Vellisco, Eduardo Márquez-Martín, Jose Luis López Campos, Ana María Rodríguez, Marta Ferrer, Pilar Cejudo, Emilia Barrot. Unidad Médico Quirúrgica de Enfermedades Respiratorias Virgen del Rocío, Hospital Universitario Virgen del Rocío, Sevilla, Spain

Introduction: We analysed the effectiveness of a high intensity behavioural-cognitive intervention compared to minimal intervention started during a hospital stay, to see if the combination of nicotine replacement therapy (NRT) can increase the quitting rate at 12 months of follow up.

Method: 2560 active smokers were studied during their hospital stay. Of these, 717 smokers refused to enter the study and after a minimal intervention they were asked if we could telephone them after one year to ask if they still smoked. The remaining 1843 smokers who received high intensity cognitive therapy were randomised to receive or not receive NRT. The follow up after discharge was carried out by outpatient visits or with telephone sessions.

Results: At one year of follow up, 7% of those who declined to enter the study had stopped smoking compared to 27% of those who entered the study (p=0.001). There were significant differences between the group that only had behavioural therapy (21% stopped compared to the group that also had NRT (33% stopped; p=0.002). In this latter group there were significant differences (p=0.03) between those who had follow up in clinics (39% stopped) compared to those who were followed up telephone sessions (30%). In the multivariate analysis, the predictors of quitting at 12 months were: to have used NRT (OR 12.2; 95% CI 5.2-32; p=0.002) and a higher score in the Richmond Test (OR 10.1; 95% CI 3.9-24.2; p<0.01).

Conclusions: A cognitive type intervention started on smokers when admitted to hospital increases quitting rates at 12 months, compared to a minimal intervention, and these rates increase even more significantly if NRT is added.
Background: Health promotion is a key component of holistic, patient-centred care. 50% of UK smokers make at least one annual attempt to quit; only 3% succeed long term. Due to the long term complications of smoking, we recognised the importance of prompt & effective SCA, a NICE (UK) priority.

The objectives of this study, in an area of socio-economic deprivation in Liverpool, were to determine whether we provide simple SCA and to explore referral rates to specialist SCA services.

Method: We undertook a 3-week prospective analysis on the respiratory wards at a large UK University Hospital (December 2010). Specialist SCA is available for all in-patients.

Results: 81 patient records were reviewed. Mean age 72 (SD 14) years; 34 (43%) male, 30 (37%) current smokers. Of these 40% received documented SCA from a GP – however, only 42% of this guidance was at time of admission. Only 43% of these smokers were referred to SCA services, of which 85% received a consultation; following this 36% continued to smoke whilst an in-patient.

Conclusion: Best practice would suggest SCA within 24 hrs of admission but this occurs in only 40% of cases. Long term follow-up of the smoking cessation rates in these patients is pending. We are working within our hospital to ensure training occurs in this area as per NICE guidance,2 aiming to reduce the burden of smoking related lung disease and have implemented a cyclical SCA education programme for all HCPs with the hope of improving SCA referral rates.


P4226 Status of the smoking cessation and its costs in eastern Mediterranean countries in 2009
Gholamreza Heydari, Tehran, Islamic Republic of Iran

Background: This study was designed with the purpose to address the situation with smoking cessation efforts and its expenditure and to provide basis for future studies and implementing tobacco control programs across countries in the region.

Materials and methods: The study was in form of questioning participating country representatives from the Eastern Mediterranean region in INB3 who were all either point individual or expert in tobacco control programs. Information needed included methods for tobacco cessation, cost of services including counseling by primary physician or specialist, gum or nicotine patch, Zyban, champix and/or missing cannabis-smoking.

Results: In 10 countries (47.6%), smoking cessation programs and counseling was directed by primary physicians. Also, 8 countries (38%) provided services through specialists. In 13 countries (63.9%), nicotine gum and in 14 countries (66.7%) nicotine patch is accessible in pharmacies. In 6 countries (28.6%), Zyban (Bupropion 150 mg) and in 7 countries (33.3%), Champix (Varnicline 1 mg) are available at pharmacists with written prescription. The mean costs of each service were higher than a pack of cigarette significantly.

Conclusion: In countries with support services for tobacco cessation, directors need to provide care at society level, less costly and accessible for everybody and in countries where such programs have not been initiated, it is recommended that effort to do so occur.

P4227 Smoking assessment & treatment in hospital: Are we providing “right care” and/or missing cannabis-smoking?
Louise Restrict, Erin Cumbus, Oliver Thomas, Myra Stern. Respiratory Medicine, Whittington Hospital NHS Trust, London, United Kingdom

Introduction: Hospital admission provides opportunities for quit-smoking advice/support. Some inpatients also smoke cannabis, which causes bullous-emphysema, but prevalence is unknown. The study aimed to determine inpatient cannabis-smoking and to measure effectiveness of our quit-smoking service.

Methods: Trainees/medical students carried out a single-day cross-sectional survey of adult inpatients, using standardised anonymous questionnaires, hospital notes and medication charts. Data was compared with previous surveys over five years.

Smoking Prevalence and Intervention Efficacy

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2008</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients interviewed (n)</td>
<td>180</td>
<td>180</td>
<td>184</td>
</tr>
<tr>
<td>Response Rate (%)</td>
<td>77</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>Smoking Status Documented (%)</td>
<td>87</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>17</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Cannabis Smokers (%)</td>
<td>17</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Advice to Stop Smoking (%)</td>
<td>53</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>NRT Offered /Prescribed (%)</td>
<td>–</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Cessation Plan Documented (%)</td>
<td>13</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

Results: 184/223 inpatients were interviewed. Cigarette-smoking prevalence was 33/184 (18%); cannabis-smoking 12/184 (6.5%). 10/33 (30%) cigarette-smokers smoked cannabis. 544 patients were interviewed over 5 years. Inpatient smoking prevalence and advice to stop smoking did not change (16.2% and 57.4% respectively). NRT prescription and cessation plan documentation increased to 44% and 35% respectively.

Conclusions: 1/3 inpatients smoke but c. 60% were given quit smoking advice despite being an evidence-based, cost-effective intervention. 1/3 cigarette-smokers also smoked cannabis. Further studies should determine the impact on health of this high prevalence. Whilst NRT and cessation plans have increased, the latter is only provided to ~40% of smokers. Further work needs to ensure effective interventions for all inpatient smokers.

P4228 Optimal cut-off point of exhaled carbon monoxide to validate self-reported smoking status in healthy adults
Juliana Zabatiero1, Demétria Kovelis1, Mahara Frontin1, Karina Furlanetto1, Leandro Mantoani1, Ercy Ramos1, Fabio Pinto1, “Laboratório de Pesquisa em Fisioterapia Pulmonar (LFIP), Universidade Estadual de Londrina (UEL), Londrina, Brazil” 2 Programa de Mestrado em Fisioterapia, Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), Presidente Prudente, Brazil

Background: There is no current consensus regarding the optimal cut-off point of exhaled carbon monoxide (CO) to distinguish smokers from non-smokers.

Objectives: To assess the accuracy of an exhaled carbon monoxide cut-off point in order to distinguish actual smokers from non-smokers among apparently healthy adults.

Methods: We studied 50 current smokers (20 male; 47±12 years; BMI: 26±4 kg/m2), with normal lung function (FEV1/FVC: 81±3), and 50 non-smokers (11 male; 44±11 years; BMI: 26±4 kg/m2; FEV1/FVC: 83±6; FEV1: 102±11l/s; pred). All subjects were submitted to exhaled CO measurement (in the group of smokers, after a mean of 10±1.2 hours of cigarette abstinence, using a portable CO monitor (MicroCO®).

Results: Median [interquartile range] levels of CO in the group of smokers and non-smokers were 10 [7-17] and 3 [2-4], respectively. The 6ppm cut-off point suggested by the manufacturer generated a 77% sensitivity and 100% specificity; however a 4.5ppm cut-off point generated the highest combined sensitivity (90%) and specificity (90%). The ROC analysis indicated that the CO monitor provided high diagnostic accuracy to distinguish smokers from non-smokers [area under the curve = 0.979 p<0.001].

Conclusions: Using a portable CO monitor, a 4.5ppm cut-off point seems more accurate than the cut-off point suggested by the manufacturer in order to distinguish smokers from non-smokers among apparently healthy adults.

P4229 Airway reactivity in inhaled mannitol in young water pipe smokers
Jérôme Schmidlin, Silvio Albusser, Michael Tamm, Daina Stolz. Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital Basel, Basel, Switzerland

Background: The inflammatory cascade related to water pipe (WP) smoking and airway hyperresponsiveness (AHR) remains unknown. We aimed to determine whether WP smoking is associated with AHR in young WP consumers.

Methods: Mannitol challenge test (Aridol® Pharmacia Ltd) was performed in acute (n=30) and chronic (n=30) WP smokers as well as cigarette smokers (CS, n=30) and life-long non-smokers (n=30). Acute exposition was defined a single episode of WP smoking ≤ 24 hours, chronic as a weekly consumption of WP for ≥ the last 4 weeks.

Results: Data of 74 subjects has been analyzed so far (15 acute and 9 chronic WP smokers, 19 CS, 31 non-smokers). Mean age was 22.6±2.4 years, 51.4% male, mean FEV1 1.26 (pns for all). CS had 5.9±3.2 PY; 35 (47.3%) had a positive allergy test. AHR to mannitol expressed by RDR differed significantly between CS and chronic WP smokers (p=0.028). The provoking dose to induce a 15% fall in FEV1 (PD15), a measure of sensitivity, was 155mg (127-176) in CS vs 315 mg (155-475) in non-smokers. The response–dose ratio (RDR) (% fall in FEV1/cumulative dose), a measure of reactivity, differed between the groups and was higher in CS vs 315 mg (155-475) in non-smokers. The response–dose ratio (RDR) (% fall in FEV1/cumulative dose), a measure of reactivity, differed between the groups and was higher in CS vs 315 mg (155-475) in non-smokers. While RDR differed significantly between CS and chronic WP smokers 0.007 [0.005-0.017], p=0.031. While RDR differed significantly between CS and non-smokers (p=0.007) and acute WP smokers (p=0.025) it did not between CS and chronic WP smokers (p=0.118).

Conclusions: Even modest amounts of cigarette smoking induce AHR to mannitol. Airway reactivity to mannitol is similarly increased in cigarette smokers and chronic water pipe smokers.
P4230
Impact of active smoking on the severity and evolution of asthma
Wiam El Kabbati, Abdelazez Aichane, Tazgha Berdala, Hicham Atif, Zouaoui Bouayad. Pulmonary Medicine, Hospital “20 Korts” CHU Ibn Rochd, Casablanca, Morocco

In adults with asthma, the effects of active smoking on asthma severity have been reported. The aim of our work is to study the influence of active smoking on asthma control. This is a prospective study spread over four years, the profile of 25 smoking asthmatic patients (group S) and 100 non-smoking asthmatic patients (group NS). The average age is 36 years in the 2 groups. There was a male predominance in the group S and female in the group NS (p = 0.00001). Asthma is isolated in 33% (group S) and 16% (group NS) (p = 0.05). Stage III is present in 65% (Group S) and 42% (group NS) (p = 0.001) and is identical for stage IV (18%). Stage I is not found in group S. Asthma is associated with rhinitis in 41% (group S) and in 42% (group NS) and rhino-conjunctivitis in 32% in both groups. Pick tests were positive in 70% (Group S) and 85% (group NS) (p = 0.01). The most common allergens are, in the two groups, Dermatophagoides Pteronyssinus and Dermatophagoides farinae. After these treatment, asthma was controlled in 55% (group S) and in 66% (group NS) (p = 0.1). We note through this work that active smoking has an impact on asthma and its evolution.

P4231
Influence of smoking on symptoms, comorbidities and severity in a population with obstructive sleep apnea (OSA) versus control
Oana Claudia Deleanu1, Diana Pocora2, Anda Elena Malat2, Ana Maria Nebunoiu2, Ion Mireles-Mazilu1, Florin Dumitru Mihaltan1. 1Pneumology III, University of Medicine and Pharmacy, “Carol Davila”, Bucharest, Romania; 2Pneumology III, Institute of Pneumology “Marili Nastu”, Bucharest, Romania; 3Statistical Laboratory, Technical University of Civil Engineering, Bucharest, Romania

Rationale: The association of smoking with OSA is uncertain, even is an association with increased upper airway resistance and predisposition to cardiovascular complications.

Method: We analyzed 129 OSA patients (65% active smokers, 35% never smokers) with normal lung function, without diurnal hypercapnia, successfully titrated with autoCPAP in lab and a control group of 17 active smokers with rhinosyn- dromy, regarding anthropometric, functional lung data, OSA symptoms, severity, comorbidities and parameters after titration. We used SPSS (T. Chi, Pearson tests).

Results: For OSA group: 22.5% female, 77.5% male, mean values: age 49.6±11.7, body mass index (BMI) 33.6±7, apnea hipopnea index (AHI) 43.1±24.2, and BHR to direct stimuli (i.e. metacholine) may be associated to an increased risk for progressive airflow obstruction in smokers. The clinical relevance of active smoking on symptoms, comorbidities and parameters after titration. We used SPSS (parametric and non-parametric tests).

Significant differences: OSA patients are less fatigue (p=0.04), have a poorer lung function (FEV1,p=0.036, FVC,p=0.040) (justified by the effects of smoking), for control group: 11.8% female, 88.2% male, age 40±12.1, FEV1 79.0±21.7, (p=0.015). The next param- eters: smoking appears not to influence symptoms, severity, and comorbidities in OSA patients, except a difficult CPAP correction of apneas. Also, smoking does not seem to contribute to the appearance of OSA and tonsilar hyper- trophy (cause of OSA). Studies are needed to thoroughly into the mechanisms by which smoking could influence OSA.

P4232
Bronchial hyperresponsiveness (BHR) to isocapnic hyperventilation of dry air (IHDA) in smokers is associated to airflow obstruction, chronic cough and β2-agonist treatment
P4233
Influence of tobacco smoking on a lipid profile
Fatiana Levina1, Julia Krasnova2, Alexander Dziinzski1, 2Therapy, Institute of Advanced Medical Studies, Irkutsk, Russian Federation; 2Gerontology, Institute of Advanced Medical Studies, Irkutsk, Russian Federation

The aim: To study influence of tobacco smoking on a lipid profile.

Materials and methods: 200 patients were examined (100 were smoking (an index of smoking ≥5 packs/years), 100-non-smokers). The mean age of the first group was 42.7±7.5 years and second -42.4±7.5 years, p=0.05. The next param- eters of a lipid profile were studied: Total Cholesterol, low-density lipoproteins (LDL), very low-density lipoproteins (VLDLs), High-density lipoproteins (HDLs), Triglycerides, Cholesterol to HDL Ratio.

Results: HDLs were revealed to be lower in 1 group in comparison with 2 group (1.32 (1.13-1.635) and 1.565 (1.331-1.785), accordingly, p=0.007). VLDLs were revealed to be higher among smoking in comparison with non-smokers (0.545 (0.39-0.935) and 0.43 (0.345-0.605), accordingly, p=0.01). Triglycerides were revealed to be higher in 1 group in comparison with 2 group (1.23 (0.865-2.065) and 0.955 (0.765-1.344), accordingly, p=0.004). Cholesterol to HDL Ratio were revealed to be higher among smoking group in comparison with non-smoking group (2.73 (1.875-2.885) and 2.35 (1.72-3.05), accordingly, p=0.039).

Conclusions: The smoking patients had higher indicators very low-density lipoproteins, triglycerides and lower indicators of High-density lipoproteins then non-smokers.


P4234
Influence of smoking on symptoms, comorbidities and parameters after titration. We used SPSS (T, Chi, Pearsons tests).

Results: For OSA group: 22.5% female, 77.5% male, mean values: age 49.6±11.7, body mass index (BMI) 29.2±7, apnea hipopnea index (AHI) 43.1±24.2, and BHR to direct stimuli (i.e. metacholine) may be associated to an increased risk for progressive airflow obstruction in smokers. The clinical relevance of active smoking on symptoms, comorbidities and parameters after titration. We used SPSS (parametric and non-parametric tests).

Significant differences: OSA patients are less fatigue (p=0.04), have a poorer lung function (FEV1,p=0.036, FVC,p=0.040) (justified by the effects of smoking), for control group: 11.8% female, 88.2% male, age 40±12.1, FEV1 79.0±21.7, (p=0.015). The next param- eters: smoking appears not to influence symptoms, severity, and comorbidities in OSA patients, except a difficult CPAP correction of apneas. Also, smoking does not seem to contribute to the appearance of OSA and tonsilar hyper- trophy (cause of OSA). Studies are needed to thoroughly into the mechanisms by which smoking could influence OSA.

P4235
Smoking exposure did not differ between the two subgroups. Smokers with BHR had worse spirometry at rest (p<0.05) and a history of chronic cough (p<0.01). Fifteen smokers regularly inhaled a β2 agonist and they all exhibited BHR, had higher bronchial toms at rest (p<0.05) and exhibited greater response to IHDA than non-treated smokers with BHR (p<0.05).

Conclusions: BHR to IHDA is common among smokers and associated to chronic cough and airflow obstruction. BHR is even more common among smokers using β2 agonists. It is not known whether this is a cause or an effect of a 12 hour interruption of β2 agonist treatment prior to challenge.

TUESDAY, SEPTEMBER 27TH 2011
7777s
Cannabis is usually inhaled and is most commonly taken in a joint containing both cannabis and tobacco. We are conducting a cross-sectional study of cannabis and tobacco smokers recruited from a primary care population in North Edinburgh. One aim of this study is to investigate whether cannabis smokers report a greater number of respiratory symptoms compared with an age and sex matched group of regular tobacco smokers. The quantification of cannabis and tobacco use is assessed by the Avon Longitudinal Study of Parents and Children and the reported respiratory symptoms by NHANES III.

We have recruited 119 subjects (Group 1) who smoke tobacco as either branded cigarettes and/or roll-your-own tobacco cigarettes) and 117 subjects (Group 2) who smoke cannabis as either branded cigarettes or cigarettes rolled in homemade sections or in cigarette papers. Only one subject used both types of products. The majority (>90%) of cannabis smokers employ unfiltered single skinned joints with 8% using bongs and a minority using other methods. The predominant form of cannabis used is resin (78%) with 22% smoking grass. Unadjusted data suggest that the prevalence of respiratory symptoms are greater at all ages and in both sexes for persons using cannabis and tobacco compared with persons using tobacco only. In North Edinburgh the majority of cannabis users smoke cannabis resin rolled with tobacco in a single skinned unfiltered joint. Respiratory symptoms typical of chronic obstructive pulmonary disease are more frequently reported by cannabis smokers than tobacco smokers and women report a greater number of symptoms than men.

Education level and smoking

Education level in the study was assessed using the Avon Longitudinal Study of Parents and Children and by examining the relationship between education level and smoking habits. Several factors were found to influence smoking, such as age, gender, and education level. The results showed that younger individuals and those with lower education levels were more likely to be smokers. Smoking rate in Georgia remains high and even tend to increase, especially among men. The prevalence of tobacco smoking and respiratory symptoms among young people and medical students. The aim of the research was to study the smoking habits and respiratory symptoms among students of medical university. The prevalence of smoking tobacco and respiratory symptoms among young adults is easily nicotine dependent and want to quit, but they have several reasons partly due to lack of programs to help them. The results showed a high prevalence of smoking among both boys and girls. Despite the brief period of smoking and its adverse effect is manifested by increased frequency of RS. These findings point to the need to strengthen prevention of smoking among young people and medical students.

P42438 Young Finnish daily smokers are experts to assess their nicotine dependence

Table 1. Distribution of Heaviness of Smoking Index (HSI) vs nicotine dependence in 523 current young smokers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HSI 0-1</th>
<th>HSI 2-4</th>
<th>HSI 5-6</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-assessment of nicotine addiction</td>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No, totally disagree</td>
<td>13 (56.5)</td>
<td>9 (39.1)</td>
<td>1 (4.3)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>- Yes, quite agree</td>
<td>1 (4.3)</td>
<td>12 (52.1)</td>
<td>5 (21.7)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>- Yes, quite disagree</td>
<td>1 (4.3)</td>
<td>1 (4.3)</td>
<td>12 (52.1)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>- I don't know</td>
<td>3 (13.0)</td>
<td>3 (13.0)</td>
<td>5 (21.7)</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

Number of quit attempts p=0.574

0 67 (31.3) 124 (57.9) 23 (10.7) 214 (100)
1 19 (25.3) 49 (65.3) 7 (9.3) 75 (100)
2 32 (42.9) 65 (86.1) 8 (11.3) 105 (100)
3 15 (20.5) 36 (49.3) 5 (7.2) 56 (100)
4 4 (5.8) 7 (9.5) 2 (2.9) 13 (100)
5 7 (17.9) 25 (64.1) 7 (17.9) 39 (100)

Conclusions: Young smokers experienced several quit attempts and were highly nicotine dependent. They also recognized their dependence.

P4239

The prevalence of tobacco smoking and respiratory symptoms among students of medical university

The aim of the research was to study the smoking habits and respiratory symptoms among students of medical university. The prevalence of smoking among medical and non-medical students in Tbilisi, Georgia: Does prevention of smoking among young people and medical students.

Smoking rate in Georgia remains high and even tend to increase, especially among young adults is easily nicotine dependent and want to quit, but they have several reasons partly due to lack of programs to help them. The results showed a high prevalence of smoking among both boys and girls. Despite the brief period of smoking and its adverse effect is manifested by increased frequency of RS. These findings point to the need to strengthen prevention of smoking among young people and medical students.
Aim: To evaluate socio-demographic and clinical characteristics associated to high levels of affective (i.e. depressive/anxious) symptoms in smokers applying for smoking cessation clinic.

Method: Current smokers applying for smoking cessation clinic at the University Hospital of Pisa were evaluated (n = 146). Socio-demographic and clinical (e.g. carbon monoxide of expired air - CO, attempts to quit, history of diseases) data were collected during their first visit. Self-administered rating scales were used to assess the level of nicotine dependence (Fagerstrom Test for Nicotine Dependence - FTND) and the level of affective symptoms (Hospital Anxiety Depression scale - HADS). Data were analyzed comparing the subjects with high HADS total score (HADS+) with those having low HADS total score (HADS-) (cut-off = 13, median).

Results: Compared to HADS- (n = 70), the HADS+ subjects (n = 76) were more likely to be female, less educated (< 12 years of school), with not executive working activity. Moreover, they had a higher rate of lifetime cancer, respiratory, psychiatric disorders, and higher CO, FTND scores. Running the multivariate logistic regression analysis adjusted for age and sex the risk to be HADS+ versus HADS- was significantly related to education (OR = 0.37, 95%CI 0.161-0.876), CO (OR = 10.53, 95% CI 1.003-10.5) and the lifetime history of psychiatric disease (OR = 2.67, 95% CI 1.206-5.893).

Conclusion: Subjects with low education, high levels of CO, and a lifetime history of psychiatric disease were at high risk to experience affective symptoms when they apply for smoking cessation clinics.


Method: Patient survey completed within the department post consultation.

Results: Of 224 respondents, self-reported smoking prevalence was 26% (53/204). 49% were correctly identified as current smokers, but only 10/26 (38.5%) were advised to stop and only 6 patients were given instructions about smoking cessation. The NRT has showed the best success rate and the efficacy of Varenicline can be increased by the combination with other therapies. The abstinence rate was: after a month 71%, 3 months 38.4%, 6 months 37.9%, 1 year 31.5%.

Conclusion: The most motivated and ready to quit smokers are the respondents with a history of smoking, healthy/sick with cardiovascular (CVD)/respiratory (RD) tobacco-related disease, using 2 questionnaires-for former smokers/active smokers regarding motivation, illness status for quitting, health status, degree of nicotine-addiction, quitting history, determinant factors for tobacco consumption. We use Excel (chi, T tests).
P4245
Making smoking cessation easier and closer the smoker: The results of Milan study of antismoking centers in pharmacies
Elena Minarini1, Aldo Mammotti2, Anna Gardiner3, Giovanni Invernizzi4, Roberto Mazzu5, Cinzia De Marco1, Roberto Bobbi6, 1Tobacco Control Unit, Istituto Nazionale dei Tumori, Milan, Italy; 2Azienda Farmaceuti Milanesi S.p.A., ADMENZA S.p.A., Bologna, Italy; 3Azienda Ospedaliera Sullite, Comune di Milano, Milan, Italy; 4Italian College General GPs, SIMG, Milan, Italy

Background: A few strong inputs from the Italian Institute of Health indicate that information and assistance to smokers are still far from being satisfactory.

Aims: To verify if offering smoking cessation at the pharmacy, a health facility where smokers have often the chance to stop, can promote the participation to cessation programs.

Methods: A 6-month pilot phase was carried out from October 2010 to March 2011. Five pharmacies in Milan were selected. Chemists were trained by the team of the Antismoking Center of the Istituto Nazionale dei Tumori (INT). Every pharmacy was equipped with informative material, CO analyzers, motivational and FTND’s questionnaires and with a clinical briefcase: moreover a trained pharmacists in the stage-of-change model of smoking cessation and INT collaborated with the chemist.

Results: In the first four months of activity 144 smokers (54% male, 46% females) asked for a consultation. The median values were: age 52 years, p31, CO 14ppm, FTND’S test 5. Regarding the pathologies, 25% of the smokers had cardiovascular and 11% respiratory diseases, 22% other pathologies, 43% declared they were “healthy” smokers. Overall, 45% of the smokers asked to stop smoking, 33% to reduce, 21% just wanted to get information.

Conclusions: The results show that the opportunity to have accessible and free smoking cessation service is considered useful by smokers. The great number of requests, together with the ease transferability of the project to other pharmacies, makes it a very promising initiative for the next future.

P4246
Nurses’ and patients’ communication in smoking cessation at nurse-led COPD clinics in primary health care
Eva Osterlund Efraïmmson1, Anna Ehrenberg2, Björn Possum3, Kjell Larsson4, Birgitta Leijon5, Neurology, Care Sciences and Society, Division of Nursing, Karolinska Institute, Stockholm, Sweden; 2School of Health and Social Studies, Dalarna University, Falun, Sweden; 3Sophiahemmet University College, Stockholm, Sweden; 4National Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; 5Neurobiology, Care Sciences and Society, Division of Nursing, Karolinska Institute, Stockholm, Sweden

Aim: To examine smoking cessation communication between patients and registered nurses, with a few days of Motivational Interviewing (MI) based education, in consultations over time at nurse-led Chronic Obstructive Pulmonary Disease (COPD) clinics in primary health care (PHC).  

Method: The first and third of three consultations were videotaped, involving 13 smokers and six nurses. In these consultations smoking cessation communication was analyzed using the Motivational Interviewing Treatment Integrity (MITI) Scale and Client Language Assessment in Motivational Interviewing (CLAMI).

Results: The nurses did, but only to a small extent, evoke patients’ reasons for change, foster collaboration and support patients’ autonomy. In the registration of specific utterances; they provided a lot of information (42%), asked closed (21%) rather than open questions (3%) and made more simple (14%) than complex (2%) reflections. Most of the registration of the patients’ utterances in the communication were either toward or away from smoking cessation coded in the category Follow/Neutral (59%), followed by utterances in the categories of Reason for change 40%, Taking steps 1% and Commitment 0%. No significant differences could be observed in the results of MITI and CLAMI between the first and third consultations.

Conclusion: Smoking cessation communication at nurse-led COPD clinics neither focused on the patients’ reasons for or against smoking nor motivated patients to express commitment to, or take steps towards, smoking cessation.

P4247
Training pharmacists in the stage-of-change model of smoking cessation: A randomised controlled trial in Sicily
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Introduction: Most pharmacists are eager to undertake an important role in health promotion but in Italy pharmacists are not trained for smoking cessation counselling.

Aim and objectives: This study set in pharmacies in Sicily has evaluate the effect of training pharmacists in the stage-of-change model of smoking cessation and motivational interviewing.

Methods: A training package based on the stage of change model of smoking cessation and motivational interviewing was carried out by University. The training was being piloted on a cross-section of pharmacy personnel. A total of 46 pharmacies have participated in the trial and attended a 3 hour training on 2008 guideline Treating Tobacco Use and Dependence. Successively pharmacists were randomly allocated by sequential allocation to the intervention or control group. The intervention group attended a 6 hour training by scheduling a initiation of training pharmacists in the stage-of-change model of smoking cessation and motivational interviewing.

Results: The study demonstrated the utility of the stage-of-change model and motivational interviewing in a pharmacy setting.

P4248
Predictors of smoking cessation within a lung cancer CT screening trial
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Background: Participating in a lung cancer CT screening may trigger smoking cessation but a clear impact on abstinence rates hasn’t been shown.

Aim: To evaluate smoking cessation in patients enrolled in a lung cancer CT screening trial (Iahung-CT).

Methods: 3004 current or former smokers (20+; pky: 55-69 yrs) from the general population were randomised in the active (CT scan, AA) or control (usual care, CA) arm of the Iahung-CT in three Italian centres (Florence, Pisa, Potenza). A postal/telephone questionnaire was administered at baseline (round 1) and at the last evaluation (round 4). Preliminary smoking data from 1186 AA subjects (94% of AA) and from 1261 CA (65% of CA) were evaluated. A paltonologist-assisted smoking cessation program (counselling & pharmacotherapy, SCP) was offered only in the Pisa centre. Multivariate logistic regression analysis was performed with smoking cessation as outcome variable. Independent variables were: sex; age (pky; 0.98 [0.98, 0.99], ≥ 1 participation in SCP.

Results: Crude cessation rates at round 4 were 21% in AA and 18% in CA (p<0.01). Smoking cessation was significantly associated to male sex (OR = 1.54 [1.54, 5.83]); ≥50; 0.98 [0.98, 0.99], ≥1 participation in SCP.

Conclusions: According to preliminary results, smokers participating in the active arm of Iahung-CT show statistically higher smoking cessation rates as compared to controls. Smokers with lung CT-detected nodules, offered of a SCP are more likely to quit smoking. Smoking cessation programs should be always offered within a lung cancer CT screening.

P4249
Late-breaking abstract: Urinary leukotriene E4/exhaled nitric oxide ratio as a predictor of exercise-induced bronchconstriction control by oral montelukast or inhaled corticosteroid
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Background: Exercise-induced bronchconstriction (EIB) is associated with vigorous physical exertion in 45 to 85% of children with asthma. A fractional exhaled nitric oxide (FeNO) and urinary leukotriene E4 (LTE4) have been used as the non-invasive markers of airway inflammation in asthmatic children. This study aimed to prove the association between LTE4/FeNO ratio and the effectiveness of therapeutic trial by leukotriene receptor antagonist or inhaled corticosteroids.

Methods: We studied 24 asthmatic children aged from 6 to 18 years with EIB, and randomized to a 4-week trial by oral montelukast (n=12) or an inhaled fluticasone propionate (FP) (n=12). A spirometry and standardized exercise challenge were performed before and after therapeutic trials. Urinary LTE4 and FeNO were measured prior to exercise challenge and 30 minutes after exercise challenge. After 4 week treatment, the same studies were conducted.

Results: After 4-week treatment, exercise performance maximum fall in FEV1, baseline and exercise-induced LTE4 and baseline FeNO were significantly diminished between both study groups; (1) %ΔFEV1: montelukast (21.00 ± p = 0.0011), FP: (23.54 ± 0.0202) (2)AUCLTE4: (0.503 ± 0.232 ± p < 0.0003), FPS: (0.527 ± 0.374 ± p < 0.012). LTE4/FeNO ratio and EIB improvement were associated with greater response to bronkukast (p = 0.082, r = 0.326) than FP for EIB treatment (p = 0.478, r = 0.274).
Background: This retrospective study was done to understand demographics and clinical course of asthmaticus treated in a pediatric critical care unit (PICU).

Methods: The medical charts of all patients above 5 years of age admitted to the PICU with status asthmaticus, at Nationwide Children’s hospital, Columbus, OH, between 2000-2007 were reviewed. Two hundred and forty seven (247) children were admitted on 281 occasions. Patients with significant co-morbidities were excluded. Final analysis was done using 222 encounters in 183 patients.

Results: The mean age was 11 years (range, 5-20 years). The mean PICU stay was 2.1 days (range, 1-15 days) and mean hospital stay was 3.6 days. Male: Female 109:74. Eighty nine (49%) were on no asthma controller medications. Adherence to therapy was noted in 124 of whom only 41 (33%) claimed compliance. 191 were known asthmatics. Asthma severity noted in 75 patients revealed 22 (29%) had mild intermittent, mild persistent 23 (30%), moderate persistent 17 (23%) and severe persistent 13 (17%). Sixty seven (37%) had a positive family history of asthma. Smoking exposure was noted in 140 (76%). Among 222 encounters, 203 received continuous albuterol, 216 received i.v. steroids, 113 receive Terbutiline, 57 received MgoSO4, 8 received non-invasive ventilation (CPAP/BiPAP) and 16 received invasive ventilation. All patients had Complications included bronchopneumonia in 25 and atelectasis in 29 patients.

Conclusion: Asthmatics with any level of disease severity are at risk for asthma exacerbations requiring PICU stay especially if they are not compliant with their medications.

P4251
The outcome of asthma among Greek children
Maria Katsara1, Fotis Kirvassilis2, Elpis Hatziagorou 2, Panagiota Marvidis2, Kalithea Koukounou1, Athanasia Marvidou2, Ioannis Tsanakas2, 1Padiatric Department, Genniminata General Hospital, Thessaloniki, Greece; 2Padiatric Pulmunology Unit, Hippokration Hospital, Aristotel University, Thessaloniki, Greece. Background: The prevalence and control of asthma among children is suboptimal. Objective: To evaluate the asthma prevalence and control of young children in the general Portuguese population. Methods: Prevalence and control of asthma-like symptoms in Portuguese young children were measured using a self-administered questionnaire (5-point Likert scale) and a postural score questionnaire (IPOS) at 6 and 12 month follow-up visits. Results: The study included 448 children (196 boys and 252 girls) aged 1 to 12 years, with 235 and 213 children having filled the questionnaire at 6 and 12 months, respectively. The prevalence of current asthma was 24.3% (95% CI: 19.4-29.2) at 6 months and 19.4% (95% CI: 14.4-24.4) at 12 months. The prevalence of atopy was 38.7% (95% CI: 33.8-43.7) at 6 months and 37.7% (95% CI: 32.7-42.7) at 12 months. The prevalence of current asthma and atopy were significantly different between boys and girls (p < 0.05). The prevalence of current asthma and atopy were significantly different between boys and girls (p < 0.05). There was no significant difference between the two follow-up visits. Conclusion: The prevalence and control of asthma-like symptoms among young children in Portugal are suboptimal. Further studies are needed to improve the control of asthma in this population.

P4252
Reproducibility of Inhalation Technique Assessment in Young Children
Shahid Sheikh1, Nadeem Khan 2, Melissa Frasure 3, Manuel Cestari 3, 1Division of Pulmonary Medicine/Pediatrics, Nationwide Children’s Hospital/Ohio State University State University, Columbus, OH, United States; 2Department of Respiratory Care, Nationwide Children’s Hospital, Columbus, OH, United States. Background: Children using metered dose inhaler with spacer have poor inhalation technique. Objective: To estimate the prevalence and control of asthma-like symptoms in children in the general Portuguese population. Methods: Nationwide, two-phase, list-assisted random-digit-dialing telephone survey (Portuguese National Asthma Survey). The first phase questionnaire was based on the GAILLEN survey. Current asthma was defined as self-reported asthma and, in the last 12 months, wheezing and/or awaking with breathlessness and/or having an asthma attack. Participants identified as having “current asthma” in first phase were re-interviewed. In addition, other children with asthma living in the same residence were also interviewed. Results: Of the 6,063 participants in the first-phase, 716 were children (0-17 years old); 143 (20.0%) had wheezing in the last 12 months; 240 (33.5%) awaked with cough or breathlessness in the last 12 months and 89 (12.4%) had an asthma diagnosis in the past. Conclusion: In-office support for asthma education improves asthma care during and following the intervention.

P4253
Assessment of Inhalation Technique: Reliability and Validity of a Checklist in Preschool Children with Asthma
Eric de Groot, Joelt Harmns, Jolita Bekhof: Amalia Children Clinine, Iusa Klinieken, Zsottle, Netherlands. Background: Incorrect use of inhaler devices has a major influence on asthma control. Objective: To assess reliability and validity of the checklist in preschool children with asthma using a metered dose inhaler with spacer. Methods: 20 children (6m-6y). All patients were treated with daily inhaled corticosteroids (ICS). The inhalation technique was recorded on videotape and independently assessed by 6 observers using the Dutch Asthma Foundation's 7-point checklist. Results: The inter-observer-agreement (IOA) was 56.5% for the checklist and 54.4% for the general impression. Conclusion: IOA of items 1-5 was good (>70%) and the general impression of the inhaler technique (1-10). This assessment was repeated after 2 weeks.

P4254
Prevalence and control of current asthma in Portuguese paediatric population
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The prevalence of "current asthma" in Portuguese paediatric population was 8.4% (95%CI 6.6-10.7); in 0-5 years old (y) was 6.5%, in 6-12y was 9.7% and in 13-17y was 8.7%.

In the second phase, 96 children with "current asthma" were included. In the last 4 weeks, 20 (22%) had night waking and 14 (15%) had symptoms more than twice a week. In the previous 12 months, 24 (25%) had a non-scheduled medical visit. 37 (39%) reported hospitalization for asthma. In the last 4 weeks, 39% used inhaled corticosteroids (21% together with LABA); 30% used leukotriene receptor antagonists.

Conclusions: Current asthma prevalence in Portuguese children is less than 10%. Most children seem to have a good short-term control of asthma, but many had ER visits and also hospitalizations related to asthma in the last 12 months.

P4255
Adolescent undiagnosed-wheeze: an unrecongnised state associated with significant morbidity, tobacco and paracetamol use
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Background: Adolescent undiagnosed-wheeze is poorly understood.

Aims: We characterised adolescent undiagnosed-wheeze hypothesising associations with behaviour-linked exposures.

Methods: The Isle of Wight Birth Cohort (UK) was recruited in 1989 (N=1456) and reviewed at 1, 2, 4, 10 and 18-years. At 18-years, "Asthma" was defined as "ever had asthma", plus either "wheezeing in the last 12 months" or "asthma treatment in the last 12 months". "Undiagnosed-wheeze" as "wheeze in the last 12 months" but "no" to "ever had asthma", with remaining subjects termed "non-wheezeers". Testing included questionnaires, skin prick tests, spirometry, bronchodilator reversibility and methacholine bronchial challenge.

Results: Undiagnosed-wheeze accounted for 22% of wheezing at 18-years. This was mostly adolescent onset with similar symptom frequency/severity to asthma. However, undiagnosed-wheeze had higher FEV1/FVC ratio (p<0.002) but lower bronchodilator reversibility (p<0.001), bronchial hyper-responsiveness (p<0.001) and atopy (p<0.001) than asthmatics. Undiagnosed-wheezeers also had higher smoking rates, earlier smoking onset and higher monthly paracetamol use than non-wheezeers (p<0.001). Multivariate logistic regression identified paracetamol use (OR 1.11, [95%CI 1.01-2.23]; p=0.03), smoking at 18-years (2.54, [1.19- 5.41]; p=0.01), family history (2.24, [1.38-5.73]; p=0.004), and asthma family history (2.26, [1.10-4.63]; p=0.03) as significant independent risk factors for undiagnosed-wheeze.

Conclusions: Undiagnosed-wheeze occurred in 5% of adolescents. It had many distinctive characteristics from asthma plus strong associations to smoking and paracetamol use that merit further study.

P4256
Asthma control test (ACT) versus intermittent oscillation system (IOS) assessment for control of asthmatic children
Malak Shaheen, Emad Mohamed, Mona El Ganzory. Pediatrics, Ain Shams Faculty of Medicine, Cairo, Egypt

Background: In spite of the great development of international guidelines for the diagnosis and the treatment of asthma, there is continuing evidence of poor control of childhood asthma.

Aim of this work was to evaluate the subjective asthma control test (ACT) against the subjective impairment oscillation system (IOS) measures of the airways resistance in asthmatic children.

Subject and methods: This study included 35 asthmatic children. All the study children were subjected to the following: full medical history, clinical examination and spirometric FEV1 measurements (to fulfill GINA assessment for asthma control) children’s assessment by ACT (using an Arabic version) was done. Finally, Impulse Oscillation test (IOS) was done to compare the objective results with the subjective results of ACT.

Results: Score 19 was the cut off value differentiating children’s asthma control (compared to the gold standard IOS cut off values). Moderate agreement between CACT/ACT test for asthma control and R5 results; kappa test = 0.54 (P=0.0001) was reported. While agreement between IOS results and GINA tool for asthma control was much less significant; kappa test= 0.36 P<0.05. Nevertheless; there was highly significant negative correlations between total scores of CACT/ACT and values of IOS results; P<0.001. The correlation coefficient for the internal consistency of the CACT/ACT was 0.89 as an evidence for ACT reliability. Also accuracy of CACT/ACT was assured by calculating area under the ROC curve (AUC) and it was 0.90.

Conclusion: This study confirms that asthma control test (ACT) is a valid and cost effective instrument for assessment of control in asthmatic children.

P4257
Parent administered questionnaire captures presence and severity of doctor confirmed wheeze in infants
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1 Respiratory Medicine, Academic Medical Centre University of Amsterdam, Amsterdam, Netherlands; 2Pediatric Pulmonology, VU Medical Centre, Amsterdam, Netherlands; 3Pediatric Respiratory Medicine and Allergies, Academic Medical Centre University of Amsterdam, Amsterdam, Netherlands; 4General Practice and Primary Care, Academic Medical Centre University of Amsterdam, Amsterdam, Netherlands

Rationale: - Infants with confirmed wheeze are at increased risk of developing asthma. Confirmation by parents is however notoriously unreliable. We aimed to combine parent reported symptoms into a diagnostic index for the presence and severity of doctor confirmed wheeze in infants.

Methods: - This study is part of the EUROPA-study, aimed at early prediction of asthma. Parents of 78 children (age 18-4 ± 5) mo) planning to consult the family doctor for acute wheezing or dyspnea scored 11 symptoms and their severity on a scale of 0 (absent) to 5 (threatening). During home visits lung sounds were recorded for confirmation by 5 pediatric pulmonologists. Wheeze severity was simultaneously scored by validated Pediatric Respiratory Assessment Measure (PRAM) (Basso/08). Presence and severity of wheeze was modelled using backwards log-linear regression combined with ROC-analysis and linear regression, respectively.

Results: - Parents established presence of wheeze correctly in 51% of the cases (AUC 0.50). A model combining nasal obstruction (p=0.067), shortness of breath (p = 0.001), activity limitation (p = 0.047) and presence of fever (p= 0.06) established presence of confirmed wheeze significantly better (AUC 0.80; p < 0.001). This integrative symptom index correlated significantly with the PRAM-score (Pear. = 0.36; p = 0.001).

Conclusion: - Accurate assessment of the presence and severity of wheezing in infants can be achieved by combining parent reported symptoms into a diagnostic model. Utilizing such an index is considerably more reliable than parent reported wheeze, and may help to guide treatment decisions and correctly phenotype subjects in research on the development of asthma.

P4258
Assessing quality of care from the patients’ and parent’s perspective in three paediatric asthma settings; a randomised controlled study in children with stable asthma
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Aim: To explore quality of care (QoC) as perceived by children with asthma and their parents in a randomized controlled study. Treatment, either by general practitioners (GP), paediatricians (PP) or asthma nurses (AN).

Methods: Children (6-16 yrs) with stable asthma were recruited from hospital practice (n=62) and from general practice (n=45). Subjects were allocated to three follow up arms (GP. PP, AN). At baseline and after 1 and 2 years, QoC was measured, by parents completing the QUOTE-CNSLD-questionnaire. By factor-analysis an adapted version was derived. Children also completed a 5-item Likert scale, independently and if needed assisted by the research nurse.

Results: The QoC dimensions of the adapted QUOTE-CNSLD-questionnaire resemble the original scales. At baseline the asthma specific quality and the child specific quality were significantly better in subjects recruited from hospital-, compared to primary care (p<0.01 in both). No significant differences in the four qualities between groups after one and two years. Correlations between child-specific quality and the parents reported qualities were poor (r=0.24, r0.19, r0.27).

Conclusions: The adapted QUOTE-CNSLD-questionnaire is applicable in a paediatric population. Two dimensions measured significant differences between children recruited from hospital care and from primary care at baseline. No difference during follow-up indicates that from a quality prospective a specialized asthma nurse is cost effective.

P4259
Quality of life in asthmatic children “a comparative study of patients’ and parents’ perceptions”
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Background: Pediatric asthma is one of the most important public health problems. Pediatric pulmonologists are not only responsible for clinical relief of children’s symptoms but also for ensuring a better quality of life for them and their families.
**P4260**

**Effects of exposure to parental smoking on pulmonary function and symptoms in children with asthma**

Polytimi Panagiotopoulou-Gartagani, Paiganiota Nikolouz, Efthimia Kalampouka, Emmanouil Karavitakis, George Kavadias, Maria Chatzisimeon, Athanasias Kadiis, Chryssa Bakoula, George Chrousos.

Objectives: To evaluate the association of exposure to parental smoking on pulmonary function and symptoms in children with asthma. Methods: Of 1086 children who were consecutively examined, 188 were excluded because of incomplete data. The children were divided according to parental smoking status (nonsmokers, occasional smokers, heavy smokers). The pulmonary function was evaluated by a spirometry test, lung volumes and airway resistance were measured by a body plethysmography test. Results: Significant differences were observed in mean FEV1 (% predicted) in children from nonsmoking and smoking households (p<0.05). In children from households with occasional smoking, a significant decrease of mean FEV1 (% predicted) was observed (p<0.05). In children from households with heavy smoking, a decrease of both FEV1 and FVC (p<0.05) was observed. Conclusions: The exposure to parental smoking is associated with a decrease in pulmonary function and symptoms in children with asthma.

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**P4261**

**Perinatal weight gain and early development of recurrent wheeze and asthma in term children**

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Objectives: To assess the association between perinatal weight gain and the development of recurrent wheeze and asthma. Methods: The analysis included 398 of a birth cohort of 411 Danish neonates born at term of mothers with a history of asthma. The primary end-points were perinatal weight gain, asthma and severe asthma symptoms. Results: Significant differences were observed in mean birth weight and mean BMI at 2 years of age in children from asthma-free and asthma cases (p<0.05). In children with asthma, a significant increase of mean BMI at 2 years of age was observed (p<0.05). Conclusions: Perinatal weight gain is associated with the development of recurrent wheeze or asthma in young-at-risk children born at term suggesting perinatal mechanisms as a common link.

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**P4262**

**Relation of asthma and body mass index in children**

Akeelah Ahmadiafshar, Sara Tabakhiiz, Zeherzeh Tobah, Behnaz Falakchakhz.

Objectives: To assess the association between perinatal weight gain and the development of recurrent wheeze and asthma. Methods: The analysis included 398 of a birth cohort of 411 Danish neonates born at term of mothers with a history of asthma. The primary end-points were perinatal weight gain, asthma and severe asthma symptoms. Results: Significant differences were observed in mean birth weight and mean BMI at 2 years of age in children from asthma-free and asthma cases (p<0.05). In children with asthma, a significant increase of mean BMI at 2 years of age was observed (p<0.05). Conclusions: Perinatal weight gain is associated with the development of recurrent wheeze or asthma in young-at-risk children born at term suggesting perinatal mechanisms as a common link.
Objective: To evaluate the level of physical activity in asthmatic children and to compare among asthma severities.

Methods: Sixty-nine children (50.1±9.1 yrs) with persistent mild (n=27), moderate (n=20) and severe (n=22) asthma were evaluated. Children wore an accelerometer for 6 days (24 h each and 2 weekends) and the total steps per day (STStr) and steps walked at either moderate or vigorous intensities (>100 steps per minute) were evaluated.

Results: Our results show that 71% of all asthmatic children were considered physically active (male=12.000 and female=10.000 steps per day). The level of activity at moderate or vigorous intensities in physically active children represented around 45% of total step counting and they showed higher activity levels during week compared with weekend days (p<0.05). The level of physical activity in asthmatic children was not related to either gender or weight. Interestingly, children with mild persistent asthma were physically less active during week days than those with moderate and severe asthma (p<0.05), however no difference was observed in the weekend days (p>0.05).

Conclusion: Congery tailor belief, most asthmatic children were considered physically active and those patients with moderate and severe asthma are still more active.

P4265

Relationships between body mass index and clinical and functional characteristics in childhood asthma: A cross-sectional analysis
Bruno Mahant 1, Nicole Beydon 2, Christophe Delclaux 1.
Characteristics in childhood asthma: A cross-sectional analysis

Background: Overweight is a risk factor for subsequent asthma in children and obesity in adults represents a unique phenotype of asthma, with more severe disease.

Objectives: To assess the relationships between body mass index and clinical and functional characteristics of childhood asthma in a cross-sectional design.

Methods: The z-scores of BMI were evaluated according to the level of control (severe exacerbation and absence of symptom in the past three months), ICS treatment and pulmonary functional tests in asthmatic children. Overweight was defined as a BMI >97th percentile.

Results: Data from 506 children (178 girls, 10.8±2.6 years, min-max [6-15]) of whom 92 (18%) with overweight were analyzed. The z-scores of BMI were increasing with age (r = 0.11, p = 0.014) and overweight was more frequently observed in girls than in boys (45% vs 33%, p = 0.045). Median of z-score were not significantly different according to atopy (p=0.31), recent exacerbation (p=0.24) or observed in girls than in boys (45% vs 33%, p = 0.045). Median of z-score were not significantly different according to atopy (p=0.31), recent exacerbation (p=0.24) or sex. The level of physical activity in asthmatic children was not related to either gender or weight. Interestingly, children with mild persistent asthma were physically less active during week days than those with moderate and severe asthma (p<0.05), however no difference was observed in the weekend days (p>0.05).

Conclusion: Congery tailor belief, most asthmatic children were considered physically active and those patients with moderate and severe asthma are still more active.

P4266

The influence of overweight/obesity on asthma symptoms among Dutch children
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Background: Overweight has been identified as a risk factor for the development and the severity of asthma in children. The prevalence of overweight in children has been increasing more rapidly in certain areas of Southern Limburg compared to the other Dutch provinces. The aim of this study was to assess the influence of overweight and obesity on the prevalence of asthma symptoms in Southern Limburg, the Netherlands.

Methods: Parents of 39,316 children (6 - 16 years) in Southern Limburg were invited to complete an online questionnaire. The questionnaire consisted of the additional questions about anthropometric variables, risk factors for asthma, and social environment. Corrections were made for the following confounders: sex, age, ethnic background, tobacco smoke exposure, birth delivery, family history of asthma, birth weight and breast feeding of the mother during pregnancy.

Results: The response rate was 23.7% (n=9,309). The prevalence of current asthma, overweight and obesity was respectively 7.7%, 15.2% and 2.5%. A high Body Mass Index (BMI) SDS was significantly related to the prevalence of current asthma (adjusted OR=1.10, 95%CI=1.02-1.19, p<0.01). Also “current wheezing symptoms” were related to a high BMI-SDS, (adjusted OR=1.10, 95%CI=1.02-1.19, p<0.01). Dry cough at night was not associated with BMI-SDS (adjusted OR=1.01, 95%CI=0.97-1.07, p=0.53).

Conclusion: There is a slight but statistically significant positive association between BMI-SDS and asthma in children in Southern Limburg, the Netherlands.

P4267

Leptin levels in obese and non-obese children with asthma
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Objective: The aim of the study was to evaluate the serum leptin levels in children with asthma and to compare it with healthy controls and to determine the relationship of leptin, systemic inflammation and lung function in asthmatic children.

Methods: The study included 62 patients with stable asthma (47 obese and 15 non-obese) and 15 healthy controls, mean age 11.2±2.85 years. All subjects were prospectively and consecutively evaluated. A skin prick test and blood sampling for assessing serum leptin levels and CR reactive protein were performed in all subjects. Body mass index was calculated using height and weight, waist circumference and waist to hip ratio measured on the same day that pulmonary function test performed.

Results: Leptin concentrations were significantly higher in obese asthmatic patients than in non-obese asthmatics and healthy controls (4.20±3.06 vs. 1.74±1.12 vs. 1.76±0.97 mg/l; p<0.001). The correlation between leptin and CRP was negative in group obese asthmatics, but without significance. The correlations of leptin with indices of pulmonary function in the study group (FEV1/FVC, PEF and PEF50%) were negative (p<0.001; p<0.05).

Conclusion: High level of serum leptin in obese asthmatic children probably is marker of exacerbated airway inflammation and influence the control and disease severity.

429. Biological correlates and comorbidities of childhood asthma/allergy

P4268

Lung clearance index differentiates children with poorly controlled asthma better than FEV1/FVC. Data from the paediatric asthma genes and environment (PAGE) study
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Introduction: Lung Clearance Index (LCI) has been shown to differ between children with and without asthma. We have further examined relationships between LCI, spirometry and outcomes within a group of asthmatic children.

Methods: Children with asthma were recruited to a national study. Assessment included respiratory and children’s asthma control questionnaires, spirometry, and LCI for individuals recruited in Edinburgh, Multiple Breath Washout (MBW). Results are compared to previously obtained data from healthy controls.

Results: 63 asthmatic patients aged 5.1-16.5 years performed MBW. Controls included 66 children aged 5.0-16.1 years. Mean (SD) LCI in our asthmatic group was 6.7 (9.9) and was higher than in our healthy group, in which LCI was 6.3 (5.0) (p=0.007). The asthmatic group also had significantly worse FEV1/ FVC z score (p<0.001), which correlated with LCI (r=-0.33, p=0.02). There was no difference in FEV1; FVC did not correlate with LCI.

Patients with completely or well controlled asthma had significantly lower LCI (6.4) than those whose asthma was described as somewhat controlled or worse (6.9; p=0.02). There was no difference in FEV1; or FEV1/FVC between these groups. LCI also correlated with reported time that asthma affected school work (p=0.36; p=0.15) and use of salbutamol (p=0.33; p=0.03).

Conclusions: Our cohort of children with asthma had significantly higher LCI compared to healthy children. LCI was also higher in patients whose parents reported poorer asthma control, something not evident for FEV1 or FEV1/FVC. LCI may be considered a better surrogate of symptom control than spirometry.

P4269

Subclinical small airway involvement in children with seasonal allergic rhinitis
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Background: Allergic rhinitis (AR) has been incriminated as a relevant risk factor for asthma onset in children and young adults. The aim of this study was to examine the presence of subclinical reversible airflow obstruction in non-asthmatic children suffering from seasonal AR.

Methods: Twenty five children with seasonal AR and pollen allergens sensitiza-
P4270  
Spirometry and measurement of airway resistance by the interrupter technique (rint) in preschool children: Influence of atopy  
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Background: Pulmonary function tests play an important role in the diagnosis, and management of respiratory diseases in children. The aim of our study was to evaluate the lung function by performing spirometry and airway resistance by the interrupter technique in preschool children in relation to their atopic status.  
Materials and methods: We studied 83 asymptomatic children (Males: 51 and Females: 32, mean age 5.15 years ± 0.72 SD). For each child has been collected the family history concerning: atopy, respiratory diseases, history of gestational and neonatal period. In all children, Skin Prick Test (SPT) to inhalant and food allergens were performed. Rint, by requiring minimal cooperation to be carried out, were performed in all subjects. Spirometry was also well tolerated by 56 subjects and was used to determine FEV1, FVC and FEF25-75.  
Results: Twenty-two subjects (26.5%) had positive SPT. The following table shows the values of the main spirometric and Rint parameters of atopic (A) and not atopic subjects (NA).  

<table>
<thead>
<tr>
<th>No. subjects</th>
<th>Atopic</th>
<th>Non atopic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (lt)</td>
<td>56</td>
<td>1.35±0.31</td>
<td>1.41±0.35</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>56</td>
<td>99.7±6.8</td>
<td>101.7±7.9</td>
</tr>
<tr>
<td>FEV1 (lt)</td>
<td>56</td>
<td>1.26±0.21</td>
<td>1.32±0.19</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>56</td>
<td>97.3±9.5</td>
<td>102.3±9.7</td>
</tr>
<tr>
<td>FEF25-75 (lt/sec)</td>
<td>56</td>
<td>1.3±0.22</td>
<td>1.33±0.26</td>
</tr>
<tr>
<td>Rint (Kpa)</td>
<td>83</td>
<td>1.12±0.31</td>
<td>1.10±0.26</td>
</tr>
<tr>
<td>Rint Kpa (lt/sec)</td>
<td>83</td>
<td>1.19±0.32</td>
<td>1.08±0.25</td>
</tr>
</tbody>
</table>

Conclusions: Despite our study assess the feasibility and repeatability of both tests in preschool children, spirometric parameters were not statistically different between atopic and not atopic children, while mean values of Rint were significantly lower in non-atopic compared to atopic children.

P4271  
Clinical correlation & evaluation of spirometry in children with asthma  
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Introduction: Spirometry is gold standard tool in management of asthma.  
Aims & objectives: To determine correlation between improvement in symptom score & lung function in pediatric asthma.  
Methods: 32 Patients were followed up over 6 months each at Pediatric Chest Clinic. Childhood Asthma Control Test was used to determine the symptom score (symptoms, daytime- & night-time cough, wheezing) & spirometry was performed at baseline, 6 weeks, 3 months & 6 months. Parents were educated about medications, techniques & compliance.  
Results: The mean age was 8.72 years (8.72±1.95, range 6-12 years) [M: F=1.67:1]. There was a 20% & 26.6% & 36.3% improvement above baseline symptom score at 6 weeks, 3 months, and 6 months (*p<0.05, Mann Whitney U test). Overall same time, there was 7.3%, 15.6% & 34.4% improvement in FEV1 and 7.2%, 12.7%, & 33% improvement in FEF25-75. At 6 weeks of treatment, there was significant improvement in symptom score with marginal improvement in lung function. At the end of 3 months, there was a significant improvement in lung function, though the improvement in symptom score tended to be more. However, at end of 6 months, all parameters showed almost same degree of improvement. The percentage improvement in score as reported by the child was comparable to that reported by parents. The improvement in FEV1 was comparable to improvement in FEF25-75.  
Conclusions: A well conducted therapeutic program with good compliance, patient education, regular medication & follow up leads to improvement in symptom score & lung function measures. The symptom score, the FEV1, and PEFR are good indicators of response to treatment in childhood asthma.

P4272  
Validation of tidal breathing analysis in the diagnosis of asthma among Filipino children aged 1 month–6 years  
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The purpose of the study was to assess the accuracy of Tidal Breathing Analysis in diagnosing asthma in Filipino Children aged 1 month to 6 years as compared with the Philippine Consensus for Asthma as a reference standard. This is a cross-sectional validation study using lung function was measured and analyzed using the tidal flow-volume loops (master screen Paed Jaeger Pediatric) in 119 sedated young children (55 males, 64 females; mean age 2.6 years) who were suspected of having asthma, before and 15 minutes after inhalation of nebulized salbutamol. The result of the Tidal Volume per kilogram (VT/kg) and the ratios of the time and volume until peak expiratory flow to the total expiratory time and volume, respectively (TPTFE/TE and VPEF/VE) were recorded. Provocation test was also done and reversibility after salbutamol inhalation was recorded.  
Results showed that the sensitivity of TBA was 36.2% and the specificity was 80.3%. The positive predictive value was 63.6% and the negative predictive value was 57.0%.  
We conclude that Tidal Breathing Analysis is a good validating device to diagnose children with asthma who can not perform the pulmonary function test. However, the test is not a reliable screening method to children still suspected to have asthma. With these findings, all clinicians dealing with pediatric patients suspected with asthma should be vigilant in diagnosing and treating children with asthma.

P4273  
Do infants with bronchiolitis get any benefit with nebulized salbutamol?  
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Background: The results of nebulized salbutamol in hospitalized infants with bronchiolitis are controversial. Rint is a standardized method of evaluation of airways broncho-constriction in infants.  
Aim: 1. To compare expiratory interrupter resistance (Rint) among 19 infants with bronchiolitis and 21 healthy controls. 2. To assess the effect of nebulized salbutamol on Rint among infants with bronchiolitis.  
Methods: Nineteen infants with bronchiolitis and positive history of atopy, family history of asthma and high total serum IgE levels were studied. Twenty one age-matched healthy infants were used as controls. Expiratory interrupter resistance (Rint) was measured before and 20 minutes after nebulized salbutamol.  
Results: 19 infants with bronchiolitis (mean age 9.25±6.34 months, 57% boys) and 21 age-matched healthy control infants were studied. 90.1% of them had eczema and 18.2% of them had milk allergy. Mean total serum IgE was 180.4±33.5 IU/mL. 82% of them had siblings with asthma, while 55% of them had a history of maternal asthma. As compared to controls, infants with bronchiolitis had significantly higher Rint. (2.6±0.4 0.78 vs 2.16±0.12 kPa L -1 second, p<0.001). Moreover, Rint was reduced significantly after administration of salbutamol: mean difference (95% confidence interval): -0.49 (-0.92, 0.06) (p = 0.028).  
Conclusions: Infants with bronchiolitis, positive family history of asthma and positive personal history of atopy might benefit from nebulized salbutamol, as shown by the improvement of Rint values.

P4274  
Exhaled breath temperature and nitric oxide in assessing children with and without respiratory disease  
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Background: The exhaled breath temperature (EBT) is a potential marker of airway inflammation. Recent data suggests a relationship between EBT and the fractional concentration of exhaled nitric oxide (FENO). Factors influencing EBT and its utility to distinguish subjects with respiratory disease are scarcely known.  
Aims: To compare EBT and FENO in patients with asthma, rhinitis and healthy children.  
Methods: In 50 subjects aged 10.3±2.8 yr (30 males), 26 with asthma, 11 with rhinitis and 13 healthy we measured the EBT plateau (EBTp, °C), FENO, spirometry at baseline and after inhalation of salbutamol, skin prick test for common allergens, questionnaires and scores for respiratory symptoms. Post-salbutamol changes (Δ pre) were calculated.  
Results: EBT and FENO correlated with age (r=0.61 and r=0.34, p<0.002; r=0.48, p<0.001). EBT correlated with FENO only in asthmatic subjects (r=0.40, p<0.05). All children with asthma and 9/11 with rhinitis had positive skin prick tests. Both EBTp and FENO were higher in asthmatic patients with reported moderate-to-severe dyspnea in the past 4 weeks in 18 asthmatic patients
without or mild dyspnea and healthy children (EBTpt: 32.4±1.6 vs 30.2±2.8 vs 30.0±3.0, p<0.05). FEV1 levels were also higher in symptomatic patients with asthma than in patients with rhinitis (48.4 ± 9.5 vs 34.7 ± 6.7 vs 11.0 ± 9.0, p<0.01). EBTpt values were not influenced by current inhaled corticosteroid therapy. **Conclusion:** EBTpt and FEV1 are influenced by subjects’ age. Both markers are useful to distinguish patients with poor asthma control from healthy patients.

**P4275**

**Bronchial provocation testing (BPT) of pre-school children by acoustic respiratory monitoring (ARM) of wheeze (Wz) and cough (C)**

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**Background:** Unequivocal diagnosis of asthma in pre-school children is limited by their inability to perform spirometry. We evaluated the feasibility of BPT using an automatic ARM system.

**Methods:** We performed doubling-dose methacholine BPT in 41 children age 2 to 7 to confirm asthma. Provoking Concentration by wheeze-endpoint (PCWz) was declared when Wz was heard by physician auscultation, SpO2 fell by 5% or respiratory rate (RR) increased by >50%. ARM of Wz and C. (PulmoTrack™, KarMeSonix, Israel) was recorded in parallel and reviewed off-line.

**Results:** Endpoint by ARM was the same as clinical PCWz in 25/41 (60.9%) and preceded PCWz in 8/41 (19.5%) patients by 1-4 doubling doses. In 4 patients (9.8%) PCWz preceded ARM endpoint and in 4 patients (9.8%) the test was inconclusive due to poor patient cooperation. Of the 4 tests where ARM lagged behind PCWz, 2 were due to ARM not detecting Wz and 2 were possibly stopped prematurely by the physician. In 6 of the patients there were false positive ARM Wz detections due to ambient noise. In 9/41 patients (22%) there was excessive cough towards the endpoint.

**Discussion and conclusion:** ARM-based BPT was as good as or better than PCWz in 90% of tests. Improved sensitivity and specificity of wheeze detection and automatic detection of increased RR are needed to facilitate physician-unattended use of the ARM for a BPT.

**Acknowledgements:** S Godfrey, N Gavrielv and the KarMeSonix Technical Team assisted in data recording and analysis. M Mierisch, RT, performed the BPTs.

**P4276**

**Relationship between H1N1 induced asthmatic symptoms and airway hyperresponsiveness in children**

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**Purpose:** H1N1 infection is known as an important aggravating factor of asthma. However, there is no report about airway hyperresponsiveness (AHR) in patients who developed H1N1 induced acute asthmatic symptoms without previous asthma.

**Methods:** We studied children less than 15 years old visited for H1N1 infection in Severance Children’s Hospital from August in 2009 to February in 2010. H1N1 infection was confirmed by real-time RT-PCR analyzing the products of nasopharyngeal swab when the patients had fever and acute respiratory symptoms like cough, rhinorrhea, and sore throat. Among the infected children, patients hospitalized due to acute asthmatic symptoms like dyspnea or wheezing sound were enrolled. We performed methacholine challenge test one month after discharge. AHR was defined as PC20 below 16 mg/mL. **Results:** Total number of H1N1-infected children was 4,362 (age of 6.95±3.75). Male to female ratio was 56.88%. Two hundred eighty seven patients (6.58%, age of 5.83±3.75) were hospitalized due to respiratory complications. Among them, 76 patients without previous asthma showed acute asthmatic symptoms (26.48%). Forty six patients were performed methacholine challenge test. Only 17 (36.96%) patients presented AHR.

**Conclusion:** H1N1 infection induced acute asthmatic symptoms not only in patients with asthma, but also in patients without previous asthma. H1N1 induced moderate to severe asthmatic symptoms might tend to be temporary and would not contribute to AHR.

**P4277**

**Malacia, inflammation and bacterial colonisation of the conducting airways in infants with persistent respiratory symptoms**

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**Department of Paediatric Pulmonology, Ghent University Hospital, Gent, Belgium; 2Department of Paediatric Pulmonology, University Ziekenhuis Brussels, Brussels, Belgium; 3Department of Paediatric Pulmonology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands.**

In infants with persistent respiratory symptoms, wet cough and wheezing de-

pite regular anti-asthma inhalation treatment diagnostic investigations to exclude underlying disease are warranted.

Prospectively 124 infants with treatment resistant respiratory symptoms were enrolled. 24 hours osseopalaeo a pH measurement and isoelectric bronchocopy (FOB) with bronchoalveolar lavage (BAL) were performed. BAL fluid was processed for neutrophil counting and bacterial culture. Inflammation of the respiratory mucosa was registered.

A 24 hours osseopalaeo pH measurement was positive in 29%. A structural abnor-
mality of the central airways was found in 47% (40% females). In 19% of infants no anatomical anomalies nor chronic inflammation of the respiratory mucosa was observed, whereas in 64% definite macroscopic mucosal inflammation was regis-
tered. Pronounced inflammation of the respiratory mucosa was associated with a significantly higher percentage of neutrophils in the BAL fluid, 48% (IQR 14 – 82) compared to 7% (IQR 0 – 16) (p<0.025) in the normal group. A positive BAL culture was found in 62% of the infants with pronounced mucosal inflammation compared to 25% in the group without inflammation (p<0.016). Fifty six percent of the BAL fluid samples was positive for bacterial culture.

In infants with treatment resistant respiratory symptoms, nearly half have anatom-
al anomalies of the central airways. In 62% of the children with pronounced airway inflammation a positive BAL culture and a significant percentage of BAL fluid neutrophils were detected, suggesting chronic bronchial infection as a possible reason for ongoing respiratory symptoms.

**P4278**

**Upper and lower airway inflammation and bronchial hyperresponsiveness in allergic rhinitis children with or without asthma**

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**Background:** Although allergic rhinitis and asthma frequently coexist, the nature of this association is still not clearly identified. **Objective:** To estimate the upper and lower airway inflammation in allergic rhinitis (AR) children with or without asthma in relation with bronchial responsiveness. **Methods:** 145 children aged 7-12 years with AR alone or AR with asthma and 35 age-matched healthy controls were observed.

Lung functions, bronchial hyperreactivity tests (methacholine and exercise) nasal and induced sputum samples were performed in all patients. Total and antigen specific IgE, IL-5, IL-10, γ-IFN levels were assessed by ELISA.

**Results:** Children with AR alone (39%) but no clinical evidence of asthma showed increased nasal and induced sputum eosinophils. Bronchial hyperresponsiveness were more significant compared with AR-alone (p<0.05).

**Conclusion:** In children with AR without asthma subclinical changes in the airways and inflammatory mediators were detected. These data support the concept of significant links between upper and lower respiratory tract involve-
ment in AR children with or without asthma and its association with bronchial hyperresponsiveness.

**P4279**

**Eosinophil cationic protein in children with respiratory allergies – When is it useful?**

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**Backgrounds:** Eosinophil cationic protein (ECF) is a secretory protein that is released from eosinophils in patients with allergic diseases. The aim of the present study was to investigate the usefulness of determination of serum ECF levels in children with respiratory allergies. Specific objectives were: (1) to assess if there are any differences in serum ECF concentrations between treated and untreated children with asthma, children with rhinitis, and children with both asthma and rhinitis and (2) if the natural seasonal exposure to sensitizing allergens is responsible for increasing serum ECP.

**Methods:** The study included treated (N=156) and untreated (N=55) children with asthma, children with rhinitis, and children with both asthma and rhinitis. Serum ECP was measured in serum collected between 8:00 and 12:00 a.m. under standardized preanalytical conditions (regarding the type of blood collection tube, time and incubation temperature during blood clotting).

**Results:** Untreated children, had significantly higher (p<0.0001) concentration of ECP [M (IQR)=35.1 (29.5-50.9) g/L] than treated children [M (IQR)=11.3 (7.1-16.1) g/L]. ECP was significantly higher during the allergen exposure season [M (IQR)=23.9 (17.6-40) g/L], than out of season [M (IQR)=8.3 (5.4-17.2) g/L, p<0.0001. **Discussion:**
Conclusions: If all limiting factors for reliable determination of serum ECP should be taken into account, determination of ECP could be helpful in objective evaluation of eosinophilic degranulation in allergic inflammation and for monitoring the effectiveness of anti-inflammatory treatment.

P4280
Chemotaxis and adhesion from peripheral eosinophils in atopic asthmatic children with and without obesity
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Background: The prevalence of obesity and asthma has increased over the past several decades. Recent investigations suggest relationship between asthma and obesity. In New Zealand, 34.5% of children are obese. The aim of the current study was to evaluate chemotaxis and adhesion of eosinophils in atopic asthmatic children and adolescents with and without obesity.

Methods: 32 obese asthmatic and non-obese asthmatic and 5 healthy volunteers were included. Peripheral blood was collected and eosinophils were purified using a Percoll gradient followed by immunomagnetic cell separator. Chemotaxis was performed with microchemotaxis chamber in triplicate with spontaneous chemotaxis (MEM) and eotaxin. Eosinophilic adhesion was calculated by comparison between absorbance of unknown samples with the standard curve.

Results: In spontaneous chemotaxis, with eotaxin and PAF, there was significant increased the adhesion of eosinophils between obese asthmatic and healthy volunteers (p<0.05). RANTES increased between asthmatic obese and healthy volunteers groups (p<0.05). Spontaneous adhesion and with eotaxin increased the adhesion of eosinophils between obese asthmatic and healthy volunteers (p<0.05).

Conclusion: This is the first study that demonstrated higher eosinophilic activity (chemotaxis and adhesion) in obese atopic asthmatic children than non obese asthmatic and healthy volunteers.

P4281
Specific IgE sensitisation in a six-year old infant cohort in New Zealand
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Aim: To determine sensitisation to infant and food allergens in 6-year old children in New Zealand.

Methods: Specific IgE (sIgE) levels were determined to 12 infant and food allergens in 659 6-year old children from Wellington (n=316) and Christchurch (n=343) from a birth cohort. Allergens tested were D. pteronyssinus, cat peel, dog hair, horse hair, cockroach, A. fumigatus, Alternaria, olive pollen, rye grass, egg white, cow's milk and peanut by a 3rd generation liquid chemiluminescent enzyme immunoassay (Siemens IMMULITE 2000). Atopic sensitisation was defined as at least one sIgE ≥ 0.35 kU/L.

Results: Sensitisation was present in 299 children (45.4%). Sensitisation to D. pteronyssinus was most prevalent with 176 children sensitised (26.7%) and with the highest sIgE levels (geometric mean: 9.1 kU/L; 95% CI: 6.2-13.2). The next highest sensitisation rate was to rye grass (141 children, 21.4%) followed by egg white (124 children, 18.8%). Mono-sensitisation was observed in 122 children (18.5%); 44 to egg white, 35 to D. pteronyssinus, 18 to rye grass, 6 to cat peel, 5 to cow's milk, 4 to peanut, 3 to horse hair, 3 to dog hair, and 1 each to cockroach, A. fumigatus, Alternaria and olive pollen. The other 177 children were poly-sensitised: 60 to two allergens, 40 to three, 26 to four, 22 to five, 17 to six, 3 to seven, 5 to eight, 3 to nine and 1 to all twelve. Of those poly-sensitised the highest sIgE level in three-quarter of these children was to D. pteronyssinus followed by egg grass.

Conclusion: Sensitisation to infant and food allergens is high in New Zealand 6-year old children with sensitisation to D. pteronyssinus the most prevalent and with very high sIgE levels.

P4282
Use of a very short protocol with no adjuvant in acute ovalbumin-sensitized allergic pulmonary response in mice for pre-clinical studies
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Many limitations have been raised over the murine models with ovalbumin (OVA) sensitization in asthma research. However, this model is still widely used as a pre-clinical study for some new specific targets for treatment. The use of adjuvant and long sensitization periods are some of the limitations we have tested whether a shorter period of subcutaneous sensitization with OVA, with no adjuvant, induces a similar eosinophilic pulmonary response in mice, when compared with previous well-established control protocols. Adult BALB/c mice were used and divided into groups, according to the number of OVA sensitzations (once or twice, OVA: 20 μg) and number (twice and 3x) and dosage (40 μg and 100 μg) of intranasal OVA challenge. The shorter protocol (10 days- length) consisted of one subcutaneous OVA sensitization and three OVA challenges (100 μg). Total and differential cell counts from bronchoalveolar lavage (BAL), eosinophil peroxidase (EPO) from lung tissue and histopathology (HE) of the lungs were performed 24 hours after the last OVA challenge. Cell counts from BAL, EPO from lung tissue and histopathological lung abnormalities were not different between the groups studied. The shorter protocol induced a significant eosinophilic lung response to OVA. We conclude that the use of one subcutaneous OVA sensitization elicits a strong allergic pulmonary response, faster than the current, a very long protocol. Our findings suggest that very short protocols with no adjuvant can be used as one of the pre-clinical tests for new drug investigations, reducing cost and time of experiments, and avoiding the use of artificial adjuvants during sensitization.

P4283
Different prevalent of allergic diseases between children allergic to cow's milk, egg and fish
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Background: Food allergy is frequently associated with other allergic diseases. Allergy to certain foods might be associated to higher risk of other allergic diseases. Objective: The aim of the study was to verify the differences in the prevalence of other allergic diseases between three groups of children allergic to cow’s milk, egg and fish.

Methods: Three groups of children aged 3 to 12, with food allergy were analyzed: Group A: cow’s milk allergy (n=55); Group B: egg allergy (n=35); Group C: fish allergy (n=20), mean age 7,3, 8.2 and 7.9. The type of manifestations of food allergy (mucocutaneous, gastrointestinal and respiratory) and the prevalence of Associated allergic diseases -bronchial asthma (BA), rhinitis (R) and atop dermatitis (AD) in each group were analysed.

Results: The mucocutaneous symptoms are the most prevalent in all groups (84%, 75% and 90% respectively). The gastrointestinal symptoms are less prevalent in group B (43%, 25% and 42%). The respiratory symptoms are more frequent in group C (8%, 26% and 60%). The coexistent allergic diseases were: in group A lower prevalence - BA: 32%; R: 42%; DA: 20%; in Group B the most prevalent allergic disease is AD (68%) with the prevalence of BA 58% and R 50%; and in contrast in Group C, BA has the highest prevalence (80%), followed by DA (60%) and R (40%). In all groups The prevalence of allergic diseases was higher than in the general pediatric population.

Conclusion: Cow’s milk allergy has lower frequency of association with other allergic diseases. Egg allergy shows a higher association with AD. Fish allergy has high frequency of respiratory manifestations and a stronger association with BA.

P4285
Investigation of asthma prevalence in the adolescents of Russian Federation
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Aim: To define the true prevalence of bronchial asthma (BA) in population of adolescents of Russian Federation.

Methods: At the first stage, according to GA2LEN protocol, in 2 research centers (Moscow and Tomsk) a continuous sample of adolescents 15-18 y.o. from own databases has been created. 12803 teenagers (5000 - Moscow, 7803 - Tomsk) have received the invitation to participate in research by post. Data of 2490 teenagers were included in statistical processing (19.5%: 1480 respondents from Moscow and 1010 from Tomsk). The average age of patients was 15.48±0.02 years.

Results: Cumulative morbidity of BA was marked at 19.9% of all respondents included in research. The analysis of prevalence of clinically diagnosed BA has shown that only 7.2% of teenagers has medical-verified diagnosis (in 2.7 times less in comparison with the cumulative morbidity of asthma). During the complex examination the number of select number of adolescents at the second stage of the study the diagnosis of asthma was verified at 5.7% of children from the group with asthma-like symptoms and at 4.9% of children without asthma symptoms according to answers in questionnaires (average index was 5.1% of adolescents in group). According to the official data asthma morbidity makes 2836,25 oo/oo. Thus, true prevalence of asthma has appeared to be 4 times less than the prevalence of symptoms registered by patients, in 1,4 times less than “diagnosed illness” according to answers of patients and in 2 times above the data of official statistics. Conclusion: Use of the standardized indices, with the further clinical screening and complex examination allows to establish true prevalence of allergic diseases.
P4286

Prevalence of allergic rhinitis in Russian adolescents
Anna Tomilova1, Leyla Namazova-Baranova1, Rasa Torshehova1, Elena Vishneva1, Ludmila Ogorodova2, Ivan Deev2, Julia Levin1. 1Allergology, Scientific Center of Children’s Health RAMS, Moscow, Russia; 2Allergology, Siberian Medical University, Tomsk, Russian Federation

The results were obtained by two centres in Russia (Moscow and Tomsk) as part of the international epidemiological study under the GA\LENN programme. The total number of participants aged 15 to 18 years was 12,830 with 2014 subjects included in the statistical analysis (1004 subjects in Moscow, and 1010 in Tomsk). The male subjects accounted for 44.6% and female subjects for 55.4%. The age was 15.48±0.02 years. The cumulative disease incidence was determined as a total of all the disease cases registered during the past year and in the previous follow-up period. Prevalence is the registered disease cases in which primary visits took place during the calendar year.

The cumulative allergic rhinitis (AR) incidence totaled 34.2%, which significantly exceeds official statistics. The female subjects indicated much more often the presence of AR compared to the male subjects (37.35% and 30.42% respectively at p<0.004). The symptoms of the ongoing AR were found in 86.45% of the total respondents who had indicated the cumulative rhinitis incidence. The follow-up results indicate significant variance from the official statistics (in 2008, the official AR incidence in Moscow was 59.2 per 100,000).

The percentage of the female subjects with AR symptoms, however, was reliably higher than that in Moscow (p=0.042), with the cumulative rhinitis incidence registered more often compared with the ongoing AR both for the entire population and for Moscow (at p=0.0125 and p=0.026 respectively). Prevalence of symptoms for allergic rhinitis was significantly higher than the diagnosed disease forms. The data obtained using standardised tools will help optimise the existing programmes for preventing and diagnosing allergic rhinitis.

430. Cystic fibrosis: clinical and laboratory studies

P4287

Pulmonary function preservation with targeted antibiotic use in infants with CF
Jacquelyn Zurbes, Carlos Milla. Center for Excellence in Pulmonary Biology, Stanford University, Palo Alto, CA, United States

We hypothesized that in CF infants microbiologic surveillance with targeted antibi- otic intervention preserves pulmonary function. Our program follows a standardized protocol with microbiologic surveillance performed at every visit by oropharyngeal sampling for culture. Positive cultures are treated based on antibiotic susceptibility regardless of clinical status. First detection of Pseudomonas aeruginosa (PA) is treated with a 6 week course of ciprofloxacin and 6 months of inhaled Colistin. Pulmonary function (PFT) is assessed by raised-volume rapid thoracoabdominal compression (RVRCT) and multi-breathe washout (MBW). Nutritional status is monitored by weight for length Z-score (WLZ). Twenty four CF infants have participated since 2008. Mean age at diagnosis was 6.8 weeks, 16 were female. On average, 75% of the cultures per patient were positive. Only 6 of the infants had at least one positive culture for PA. In contrast 75% of the infants had at least one positive culture for S. aureus. By RVRCT parameters only 4 infants had evidence for significant obstruction. However by MBW almost all had evidence for mild ventilatory inhomogeneity (mean LCT 8.5±1.1). No correlation was found between RVRCT and MBW parameters. We did find an inverse correlation between WLZ and LCI (r=0.46). Further, we found no relationship between microbiologic results and PFT parameters. Patients with positive cultures, including those with PA, had comparable PFT results to those not infected. Thus, despite airway colonization with CF pathogens, there was no evidence for significant detrimental changes in lung function. We propose that frequent monitoring and targeted use of antibiotics preserves lung function in infants with CF.

P4288

KL-6 serum levels in adult cystic fibrosis patients
Federico Piffer, Andrea Airoldi, Marta Di Pasquale, Giovanna Pizzamiglio, Maddalena Zanardelli, Samanta Galbiati, Barbara Dallari, Francesco Blasi. Dipartimento TORACO-Pulmonare e Cardiocircolatorio Università degli Studi di Milano; Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy

Introduction: Cystic fibrosis (CF) is a chronic lung disease with a typical ob- structive pulmonary pattern. KL-6 is a high molecular weight glycoprotein, whose serum level are related to alveolar epithelium damage particularly in interstitial lung diseases; its role is not clear in CF patients.

Objective: To compare C-reactive protein (CRP) and KL-6 levels in adult CF patients requiring intravenous antibiotic therapy or pulmonary exacerbation.

Methods: Prospective observational study of adult CF patients admitted with pulmonary exacerbation to CF Adult Unit of Policlinico Milan, between November 2009 and February 2010. KL-6 and CRP serum levels were measured on admission, at day 7 and day 14 of intravenous therapy. Clinical and functional data were collected.

Results: 13 patients were analyzed (mean age 33 yrs, range 24-44, 6 women). Mean FEV1 was 49% of predicted (range 25-70). KL-6 levels seemed to show a trend similar to CRP’s during hospitalisation, with early increase and late decrease of the mean values.

Conclusion: These preliminary data show that KL-6 could be an useful biomarker in the follow-up of pulmonary exacerbation of adult CF patients. Further studies in greater cohorts are needed in order to confirm these data.

P4289

Six minute walk test in children, adolescents and young adults with and without cystic fibrosis
Fabiola Mester Pereira, Maria Angela Ribeiro, Adelyda Dalbo Toro, Gabriel Hessell, Antonio Fernando Ribeiro, José Dirceu Ribeiro. Department of Pediatrics, State University of Campinas, Campinas, São Paulo, Brazil

Background: The six minute walk test (6MWT) analyses tolerances to submaximal effort. It’s important to compare Cystic Fibrosis (CF) patients with healthy controls to better understand their responses to physical exercise.

Objective: To evaluate patients with CF submitted to 6MWT and compare them to a control group (CG).

Methods: Transversal, prospective study comprising patients from a Brazilian CF reference centre. 6MWT was applied in a group of CF patients and in healthy controls accordingly to ATS guidelines and repeated after 30 minutes of rest. Respiratory frequency (RF), heart rate (HR), oxygen saturation (SpO2), dyspnea index, nutritional status and spirometry values were analyzed. Patients on pul- monary exacerbation were excluded from the research. Spearman’s correlation and ANOVA for repeated measures were used, p<0.05.

Results: Fifty-five CF patients and 185 healthy individuals participated (12±4.3 and 11.3±4.3 years, respectively). CG walked a greater distance than the CF patients in both tests (6.6±5.3±4 m x 547.2±80.6 m and 616.5±58.0 m x 552.2±82.1 m; p<0.0001). Walked distance correlated with age, weight and height. Both groups achieved similar distances in both tests, although CF patients had bet- ter performance in the first test. Learning effect was not seen. The ICC calculated between the two tests was 0.81 and 0.77 (CF and CG, respectively). The SpO2 maintained stable during the test, with an increase in HR and RF (p<0.0001) in all individuals.

Conclusion: CF patients presented functional impairment when compared to control group. Repeating 6MWT may represent an unnecessary effort for patients with chronic pulmonary disease.

P4290

Exhaled breath temperature in adult cystic fibrosis
Gabriel García1, Noemí Granero1, Berta Hendriksen1, Deleo Carlos1, Bujar Erzeguević1, Miguel Bergna2. 1Neumology, Hospital Rodolfo Rossi, La Plata, Bs As, Argentina; 2Neumology, Hospital Antonio Cetrángolo, Vicente Lopez, Bs As, Argentina

Cystic fibrosis (CF) is characterized by chronic airway infection and inflammation, which accounts for most morbidity and deaths. It has been suggested that inflated airways may increase the exhaled breath temperature (EBT), however, patient with Cystic Fibrosis (CF) may have of the opposite effects. The aim of this study was to measure exhaled breath temperature in adult CF patients by comparison with healthy controls. Fifteen adult CF patients examined (8 female, mean age 28.6±7 years, VEF1% 44.4±21%) and 15 healthy persons (7 female, mean age 34±3 years) were recruited for the control group. The measurements of exhaled breath temperature (EBT) were performed with a second generation hand-held device (X-Halo, Delmedical Investments LTD Singapore) using an antibacterial filter (Clear Advantage, Creative Biomedics, Inc).

Mean value of EBT in controls was 33.80±0.87°C and EBT mean value in adults CF patients was 33.53±0.73°C, the difference was not significant (p=0.05). We conclude that patients with CF had EBT similar to healthy people, contrary to the asthmatics patients, possible due to chronic epithelial cell damage, increased mucosal barrier and the reduce of the vascularity.

Conclusion: To compare C-reactive protein (CRP) and KL-6 levels in adult CF patients requiring intravenous antibiotic therapy or pulmonary exacerbation.
Detection of volatile hydrogen cyanide released by Pseudomonas aeruginosa with cavity ring down spectroscopy
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Pseudomonas aeruginosa (Pa) produces hydrogen cyanide (HCN) which discriminates from other common CF lung pathogens. HCN production is supposedly increased under microaerobic conditions, which characterizes the habitat of Pa in vitro. This implies a potentially interesting marker in detecting Pa respiratory infections. Laser-based cavity ring down spectroscopy (CRDS) offers high sensitivity and molecular specificity in detecting trace gases and is suitable for incorporation in handheld devices.

In this in vitro study we aimed to assess the feasibility and reproducibility of measuring HCN production through CRDS, and to determine the optimal oxygen concentration for cyanogenesis from Pa cultures on agar media.

A state-of-the-art CRDS was used to assess HCN online concentrations from the head space of Pa grown in petri dishes. Twenty-four hours prior to the experiments Pa was grown on Muller Hinton media and grown in ambient air at 37°C. From start of the experiment, cultures were flushed with adjustable flow of 0.01%, 1%, 10% and 21% O2, diluted in pure nitrogen.

HCN production was measured well above the detection limit from Pa cultures using CRDS (table1).

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<th>Headspace oxygen (%)</th>
<th>N</th>
<th>Median HCN release [range]</th>
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<tr>
<td>0.01</td>
<td>38</td>
<td>39 (11–1227)</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>44 (9–778)</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>10 (2–57)</td>
</tr>
<tr>
<td>21</td>
<td>12</td>
<td>11 (11–80)</td>
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</table>

HCN may serve as a sensitive marker for presence of these bacteria, well above the detection limit. Intra-experimental variation coefficient was 21%. HCN production was highest in low oxygen concentrations (p<0.001).

HCN production can be measured using CRDS, and is affected by oxygen concentration. HCN may serve as a sensitive marker for presence of these bacteria.

Methods:
A cross-sectional analysis of 307 CF patients, we compared the group of once only infected (OI) to chronically colonized patients (CC). We analyzed differences in age, lung function and BMI z-score. Subanalysis included group of once only infected (OI) to chronically colonized patients (CC). We compared them with Pa culture results, to determine their role in early diagnosis and follow-up, to correlate them with severity of disease and to determine factors which cause antibody positivity. Ninety CF patients were included; they were divided into chronic, intermittent, control and mucoid Pa groups according to their airway cultures. They were evaluated in each 3-6 months in total 4 visits in a follow-up period of 2 years. In each visit, Pa antibodies against exotoxin, elastase and alkaline protease were determined in blood by ELISA method. The presence of at least one antibody had the highest sensitivity. Among the antibodies, alkaline protease had the highest specificity and elastase had the highest sensitivity. All antibodies were highest in mucoid group followed by the chronic group. Antibodies were higher in the chronically colonized patients than the noncolonised ones. Elastase was highest in the chronic and lowest in the mucoid Pa group. The presence of antibodies were much higher than positive Pa cultures in patients younger than 5 years of age. Only in mucoid group, there was a negative correlation between FEV1 and alkaline protease. In CF, Pa antibodies can be considered as early markers for diagnosis especially in young children who can not expectorate, however, anti-Pa antibodies should be used together with sputum cultures for long term follow-up and treatment.

Introduction: In recent years there has been an increasing number of recognized emerging pathogens like Stenotrophomonas maltophilia (SM) and Achromobacter xylosoxidans (AX) but their effect in CF lung disease is yet unknown. Aims: 1) to assess the prevalence of SM and AX and 2) to compare the lung function, clinical symptoms at first isolation, CT scan and colonization with Pseudomonas aeruginosa (PA) between the two groups.

Results: 130 patients were included in this study, 44 of whom (33.8%) had a positive culture to SM and 11 (8.4%) to AX at some time. Mean age at acquisition of SM was 6±4.6 years and of AX was 6.5±3.8 years. In the SM group 36% were patients were under 4 years in age compared with 9% in the AX group. No significant difference in symptoms at acquisition (56% and 63% respectively), FEV1 (75% and 84%), bronchiectasis (47% and 36%) and PA colonization (79% and 91%) were found between the SM and AX groups. After specific ABT therapy, chronic colonization was higher in AX (36%) in comparison with the SM group (9%). Conclusion: The prevalence of SM colonisation is higher than AX. Patients colonized with SM were younger but chronic infection was more associated with AX.
Preventable deaths and better outcomes in CF: Need for organising care at Pulmonology, Moscow, Russian Federation; Cystic Fibrosis, Research Centre for Natalia Kashirskaya, Nikolay Kapranov. The genotype-phenotype relationship in cystic fibrosis (CF) patients is a developing country. Development of programs aimed to increase knowledge and complexity of factors that characterize transition to European standards in Conclusions: 66% prevalence of del F508. 15 deaths were encountered, 67% before 2004 when complications). Mean age at diagnosis was 1.3 years, 36/45 were genotyped with 66% prevalence of del F508. 15 deaths were encountered, 67% before 2004 when the Ministry of Health provided funding. 66% of deaths before the age of 3 years, were influenced by poor socio-economic status, undernutrition and reduced level of understanding of the nature of the disease. 65% of patients developed premature severe lung disease related to poor nutrition and early acquisition of P aeruginosa. CF related conditions as ABPA, CFRLD, diabetes in 64/55 patients represented risk factors for poorer outcomes. In 55% of patients malnutrition was correlated with poverty. The level of funding represented only 50% of the needs and the lack of a staffed CF unit was a major barrier to proper care of patients. Clinical outcomes were adversely impacted by lack of funding and complexity of factors that characterize transition to European standards in a developing country. Development of programs aimed to increase knowledge and motivation for being involved in CF care are needed in order to offer better outlooks for CF patients. Genotype-phenotype correlation in cystic fibrosis patients bearing a novel complex allele Riccardina Tesse, Angela Polizzi, Teresa Santostasi, Anna Diana, Antonio Manca, Vito Paolo Logrillo, Luciano Cavallo. Department of Biomedicine of the Developmental Age, University of Bari, Bari, Italy Objective: The genotype-phenotype relationship in cystic fibrosis (CF) patients bearing a novel transmembrane conductance regulator (CFTR) complex allele was investigated. Cases report: During the genetic characterization of 289 CF Caucasian patients [MF ratio 0.9:1, median age 16 years (range 1–46)] we found a new complex allele [H939R,H949L] in five unrelated male patients (age range 15-25 years). They all carried two CF-associated mutations, H939R and B494L, on the same exon 13 of CFTR gene in one allele, and had R245T, G542X, 1259naA, G1349D and F508del, respectively, in the other allele. All subjects had abnormal sweat chloride test values. The patient with R245T/[H939R,H494L] genotype presented CF-related symptoms restricted exclusively to hepatopathy with high levels of transaminases, but a good nutritional status and pancreatic sufficiency. The other four patients had signs of classic CF, including chronic lung and sines disease, recurrent respira- tory infections, failure to thrive and pancreatic insufficiency. Particularly, patient with 1259naA/[H939R,H494L] genotype presented with meconium ileus, and the subject bearing F508del/[H939R,H494L] showed the most severe pulmonary manifestation of CF with abnormal values on tests of lung function. Conclusion: Our findings suggest that the allele [H939R,H494L] greatly reduces the residual function of CFTR if on the other allele is present a severe mutation (i.e. G542X, 1259naA, G1349D and F508del), determining a very low residual function, the combined effect being an overall reduction of CFTR function; on the contrary, when the other allele carries a mild mutation, such as R245T, the overall effect is a cumulative better CFTR functioning. Genotype-phenotype correlation in cystic fibrosis patients bearing a novel complex allele P4297 Twentieth years of care for CF patients in Moscow region of Russia Stanislav Krasovsky, Alexander Chernikov, Elena Amelina, Anna Voronkova, Natalia Kashirskaya, Nikolay Kapranov. Cystic Fibrosis, Research Institute of Pulmonology, Moscow, Russian Federation; 3Cystic Fibrosis, Research Centre for Medical Genetics, Moscow, Russian Federation Objectives: The aim of the study was to assess the median survival age of the patients in the Moscow region of Russia, followed in children and adult CF Centers of Moscow during the period 1991-2000 and 2001-2010, the proportion of adults and gender differences in the survival, if any. Methodology: A database of CF patients was started in 1990. The diagnosis of CF was confirmed by positive sweat test and/or genetic analysis, or neonatal screening (started in 2007). On January 1 2001 there were 185 patients registered in Moscow region, 371 patients were followed in children and adult CF Centers of Moscow during the period 2001-2010. Results: Of 185 patients (98 males), followed during 1991-2000 yrs, 23 (12.4%) have died (7 males, the mean age at death was 18.1±9.2 years), 162 (87.6%) patients were alive on January 1 2001 (mean age 11±3.6 y). The median survival was 25.69 years. Significant gender difference in median survival was noted with 27.3 years for male and 25.1 years for female patients. The proportion of the patients over the age of 18 was 18.9%. During 2001-2010 of 371 patients, 45 (12.1%) had died (26 males, the age of death ranging from 4 months to 40 years; the mean age at death was 16.8±8.4 yrs); 326 patients were alive (mean age 13.2±9.6 yrs). The median survival age increased significantly - 35.71 years (p=0.045). There was no significant gender difference in the survival rate. 32.6% of adult patients – a significant difference since 1991-2000 (p<0.05). Conclusion: A large increase in the Moscow Region CF patients' survival and number of adults was observed during 12 years of specialized treatment, performed in Moscow centers, pointing out a survival advantage of specialized care. Phenotype and genotype in adult patients with cystic fibrosis in Uruguay Alejandra Rey, Gabriela Rutz, Pacheco Ediberm, Guicamburi Rosarios, Maria López Varela, Hospital Matern. Universidad de la República, Montevideo, Uruguay; Unidad Adultos de Fibrosis Quística, Banco Prevención Social, Montevideo, Uruguay. There is insufficient knowledge on Cystic Fibrosis (CF) in many countries; patients are often treated inadequately. Life expectancy is consequently far below what could be attainable with adequate treatment. Therefore it is very important to train Centers to concentrate clinical experience on diagnosis and management of disease. In June 2010, the Uruguayan Parliament created the First National Reference Center for Diagnosis and Treatment of Patients with Cystic Fibrosis. Objective: To describe genotypic and phenotypic characteristics of patients at the time of first encounter at a CF Center for adults in Uruguay. Methods: CF patients over 14 years were evaluated with medical history, spirom- etry and spumor studies. Results: 41 adults entered the center. Mean age was 23.9±8.4, mean age at diagnosis was 14.2±11.3 years. Colonized patients showed differences with non- colonized in: mean age (25.8 ± 22.0 vs. 20.1±0.1), mean age at diagnosis (13.4±11 vs. 14.4±11, p=0.01), lung function: FVC (84% vs. 95%, p=0.01); FEV1 (68% vs. 88%, p=0.00) and history of hemoptysis. Genetic mapping for 30 patients indicated that: 30% had two CFTR mutations, 36% a single mutated allele detected and in 53% no mutations detected. The most common mutation was ΔF508. The remaining mutations were substantially heterogeneous. In all, we had 3 alleles mutation class 1, 13 class 2, 3 class 4, and 1 class 5. Conclusions: - Colonized patients were diagnosed earlier in life, showed significant deteriora- tion in spirometric measures and more frequent hemoptysis. - Our population had different types of CFTR mutations. - The mutation ΔF508DEL was the most common and present in 16%. - 33% of CFTR mutations were not detected.
P4302 Evaluation of disease knowledge in children with cystic fibrosis and their families

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Introduction: Increasing the disease knowledge of patients with cystic fibrosis (CF) and their families is important for treatment adherence.

Aim: To determine the knowledge levels and associated factors in CF patients and their families.

Methods: Parents of 82 CF patients and 39 children >10 years followed at Paediatric Pulmonology Division were included in the study. Knowledge levels were evaluated with a standardized questionnaire which assesses 3 domains of knowledge: respiratory, digestion and nutrition. Knowledge was compared with demographic features and disease severity determined by Shwachman-Kulczycki Scores (SKS) and pulmonary function tests (FEV1%).

Findings: 82 patients were included to the study (44 girls; median age: 9.5 years [25-75percentiles: 5.1-14.1]). Median follow up was 8.0 years (25-75percentiles: 4.6-11.4). Median SKS was 75”good” (25-75percentiles: 55”good”- 85”good”). Mean FEV1% was 66.5±28.0. Knowledge level was 65.8%±14.7 for children and 69.9%±14.6 for families. Children’s knowledge increased with age (p<0.04), but there was no relation with children’s age and family knowledge. Although no correlation was found with children’s knowledge and socio-economic status (SES), families’ knowledge was related with SES (p<0.04). There was no relation with disease severity and children’s or families’ knowledge. Knowledge level was higher for patients who were followed for longer period at our clinic (p<0.04). Knowledge of children or families were not related.

Conclusion: CF patients’ and their families’ knowledge are fairly good but needs improvement. Families’ knowledge is associated with SES Knowledge of children increases with age and follow up time, but is independent from family knowledge and SES.

P4303 An audit to assess the value of the MDT approach in patients in a UK CF unit

Manish Gautam1, Abdul Ashish2, Martin Ledson2, Josheel Naveed1, and SES.

Background: It is widely accepted that in CF best patient and family care should involve a well co-ordinated multidisciplinary service. However, the interdisciplinarity effectiveness of the team, including the patient’s perception of their team is rarely assessed.

Aims: We performed this study in order to evaluate the performance of our local CF MDT from an objective and patient perspective.

Methods: “On the spot” questionnaires were distributed to MDT members, who had worked with the unit for over one year. Questions were related to the knowledge of 15 randomly selected CF patients regarding their microbiology, FEV1, transplant status, social history, portacath, compliance issues and insulin therapy.

Results: Table 1 shows knowledge of MDT members about their patients

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<tr>
<td>85%</td>
<td>83%</td>
<td>85%</td>
<td>85%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Average scores and ranking

Conclusions: Results confirmed CF patients often form close rapport with specialist nurses and associate Consultants with important decision making related to their care. Interestingly, doctors and CF nurses scored equally well in patient knowledge and only marginally above others. These results suggest an effectively functioning MDT whilst highlighting the often under recognised value of individual specialties.

P4304 Improved turn around time for molecular genetic analysis for cystic fibrosis: The Irish experience

Frances Flanagan, Louisa Glackin, Dubliffeasa Slattery. Respiratory, Children’s University Hospital, Dublin, Ireland

Introduction: Ireland’s Cystic Fibrosis (CF) newborn screening programme is due to commence later in 2011 using immune reactive trypsinogen & genetic analysis for the detection of cystic fibrosis transmembrane regulator protein (CFTR) mutations. The National Centre for Medical Genetics screens for 11 CFTR mutations & a further analysis for rarer mutations is currently performed at Brompton (using gene sequencing & multiplex ligation-dependent probe amplification (MLPA) testing). Prior to 2008 this further analysis was performed in Exeter & subsequently in Brest.

Aim: To identify the turn around time for genetic analysis results for children with suspected CF

Method: A 16 year retrospective study of genetic analysis results for CFTR mutations was performed. The turn-around time was defined as the number of days from sending DNA until reports were received. Descriptive statistics were used.

Results: Overall, the median time to receive genetic analysis results was 23 days, range 1-2343 days (n=91). The median turn-around time for the identification of 2 positive CFTR mutations was 21 days, range 1-1973 days. The most common identified mutation, Phe508del/Phe508del, had the shortest median turn around time of 18 days, range 1-107 days. Three patients initially suspected of having CF & with 2 positive sweat tests, did not have any CFTR mutations identified (median time 2252 days, range 229-2434 days). The National Centre for Medical Genetics screens for 11 CFTR mutations & a further analysis for rarer mutations is currently performed at Brompton (using gene sequencing & multiplex ligation-dependent probe amplification (MLPA) testing). Prior to 2008 this further analysis was performed in Exeter & subsequently in Brest.

Conclusion: Recent technological advancements allow for more detailed genetic analysis to be performed, identifying newer CFTR mutations over a shorter time period. The introduction of newborn screening & extended CFTR genetic analysis will ensure that the time to CF diagnosis is greatly improved.

P4305 Validation of the Spanish version of the Leicester cough questionnaire in children with cystic fibrosis

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Background: Cystic Fibrosis (CF) patients present chronic inflammation with a mucus thickness and decrease ciliar mobility, causing chronic cough, bacterial colonization and respiratory infections. Cough is one of the most important symptoms for CF and it is directly related to exacerbations. Also, represents an upset that adverse quality of life and social relations.

Objective: Validate the Spanish version of the Leicester Cough Questionnaire (LCQ) in CF.

Methods: After the adaptation to Spanish, the sample was selected by 58 CF patients from Corporacio Parc Taulí and Asociacion Madrilena Contra la Fibrosis Quistica, Spain. The questionnaire was administered twice in stable disease patients in order to contrast the results.

Results: Patients characteristics: age 11.7 (3.1) years, BMI of 19 (13) kg/m². Total LCQ1 18.46 (2.4) vs LCQ2 18.69 (2.3) (p=0.769). Cronbach alpha coefficients was: LCQtotal (0.86) and for the domains: LCQphysical (0.76); LCQpsychological (0.79) and LCQsocial (0.78). The ICC was: LCQphysical (0.82), LCQpsychological (0.75), LCQsocial (0.63) and LCQtotal (0.83) (p<0.01 all). We observed moderate correlations with specific quality of life questionnaire (CFQ-R): respiratory symptoms CFQ-R14 (r=0.51) and CFQ-Rchild (r=0.67) (p<0.01, both) and with pulmonary function, PVC and FVE1. LCQphysical (0.42 and 0.48); LCQpsychological (0.60 and 0.62) and LCQtotal (0.55 and 0.58), all significant (p<0.05).

Conclusion: The Spanish version of the LCQ is reliable and valid for CF patients, in which it has observed relations between quality of life and pulmonary functions. Sponsored by: Proyecto AVANZA, TSI-020110-2009-431. Ministerio de Industria Turismo y Comercio, Spain.

P4306 Downregulated BMPR2 signaling pathway in nitrofen-induced pulmonary hypoplasia

Marine Makanga, Celine Devwatcher, Bento Rondelet, Robert Naeije, Laurence Devwatcher. Physiology Laboratory, Université Libre de Bruxelles, Brussels, Belgium

Background: Despite remarkable progress in resuscitation and intensive care, morbidity and mortality in congenital diaphragmatic hernia (CDH) remain high due to severe pulmonary hypoplasia. However, pathogenesis associated with CDH is still not clearly understood. The bone morphogenetic protein receptor (BMPR) type 2 signaling pathway plays a crucial role in fetal lung development.

431. Issues in paediatric and neonatal intensive care

TUESDAY, SEPTEMBER 27TH 2011
Hypothesis: We sought to determine whether BMPR2 signaling pathway is altered in the nitrofen-induced pulmonary hypoplasia associated to CDH.

Methods: Pregnant rats were exposed to either 100 mg nitrofen or olive oil on day 9 (D9) of gestation. At D17 and D19, embryos were delivered by cesarean and sacrificed to check if diaphragmatic hernia existed. Fetal lung, heart and liver tissue weights and body weight of each fetus were recorded. Lung tissue was harvested for pathological evaluation (by immunohistochemistry and RTQPCR).

Results: Lung, heart and liver weight-to-body weight ratios decreased by 20, 30 and 25% (p<0.05) at D17 and by 25, 15 and 25% (p<0.05) at D21. In the CDH group, at D21, the airway septa were thicker and the radial alveolar count was significantly lower compared to controls. In the lungs, gene expression of BMPR2 was decreased in the nitrofen group at D17 and D21, together with decreased gene expression of the DNA binding protein 1 (Ddx1), the major target of the BMP signaling pathway. At D17 (but not at D21), pulmonary gene expression of gremlin, a BMPR antagonist, was increased, while pulmonary gene expression of BMP4, a BMPR agonist, decreased.

Conclusions: In nitrofen-induced CDH, BMPR2 signaling pathway is downregulated in hypoplastic lungs at both early and late stages of lung development.

P4307
Rho-kinase inhibitor ameliorates bleomycin-induced chronic lung injury in neonatal rats
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Bleomycin (BLEO) induces a chronic neonatal lung injury (CNI) in rats that is characterized by inflammation, arrest of lung development and pulmonary hypertension (PHT), similar to severe bronchopulmonary dysplasia. Increased Rho-kinase (ROCK) signaling contributes to experimental inflammatory lung injury in adult animals but its role during early life remains unknown.

Methods: Rat pups received BLEO (1 mg/kg/d i.p.) or saline vehicle from postnatal days 1-4 (Y27632 (a ROCK inhibitor); 10 mg/kg/d i.p.). Inflammation was assessed by tissue scores of immune-inflammatory macrophages (CD68) and neutrophils (MPO). Chronic PHT was assessed by right ventricle/left ventricle+septum weight ratio and% medial wall thickness of pulmonary resistance arteries. Markers of lung growth, injury and alveolarization included weight, tissue fraction, mean linear intercept and secondary crest counts.

Results: Lungs of BLEO-exposed pups had up-regulated ROCK activity, as evidenced by increased phosphorylation of ROCK targets, MYPT-1 and LIMK1, which was maintained till Y27632. Treatment with Y27632 completely prevented neutrophil influx to the BLEO-exposed lung while having no effect on increased macrophages. Y27632 completely prevented BLEO-induced PHT and partially improved septal thinning, but did not affect inhibited lung growth or alveolarization. Complete abrogation of BLEO-mediated neutrophil influx by treatment with SB265610 (a CCR2 antagonist; 4 mg/kg/d) had no effect on parenchymal or vascular injury.

Conclusions: ROCK inhibition prevented chronic PHT and improved parenchymal injury (septal thinning) in BLEO-mediated CNI, independent of changes in inflammatory cells. Funded by the CIHR.

P4308
Characterization of miRNAs circulating in sepsis patients’ serum
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Background: MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate miRNA expression at the post-transcriptional level and thereby regulate fundamental biological processes. A number of methods, such as multiplex polymerase chain reaction microarrays, have been developed to profile the levels of known miRNAs. However, these methods cannot identify novel miRNAs or accurately determine their expressions over a range of concentrations. Deep sequencing methods provide a suitable platform for genome wide transcriptome analysis and can identify novel transcripts.

Methodology/Principal findings: We isolated total RNA from serum samples of 9 sepsis patients. We sequenced circulating miRNAs in small RNA libraries using Solexa sequencing. This revealed a total of 154 known mature and 25 mature-star sequences, and predicted 38 novel miRNA candidates. The miRNA expression profiles of sepsis patients were different from those of healthy controls previously reported by Chen et al. The uniquely biased distributions of nucleotides may be related to the stability of circulating miRNAs.

Conclusions: Some of these novel candidate miRNAs may be specific to sepsis patients and could be used as biomarkers to evaluate sepsis prognosis by measuring their levels in blood. Follow-up studies on the functional roles of these novel miRNAs and identifying their targets should provide additional insights on the development and progress of sepsis.

P4309
Spontaneous respiratory activity during mechanical ventilation of term born infants
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Aim: Prematurely born infants frequently breathe while being mechanically ventilated and the pattern of the respiratory interaction influences outcome. The different interaction patterns seen are the result of stimulation of respiratory reflexes (Cheyne-Stokes, the Hering-Breuer reflexes). Respiratory reflexes may be weaker in term born compared to prematurely born infants and thus may not influence the outcome of the former. The aim, therefore, of this study was to characterise any spontaneous respiratory efforts of mechanically ventilated infants born at term.

Methods: To date, ten infants (median gestational age 38 weeks) have been studied at a median postnatal age of five days: five infants on intermittent positive pressure ventilation (IPPV) and five on synchronised intermittent mandatory ventilation (SIMV). Oesophageal, gastric and airway pressures, flow and volume were simultaneously recorded for at least 20 minutes, 100 consecutive breaths were analysed for each baby.

Results: All the infants breathed during mechanical ventilation. Four patterns of interaction were noted: synchrony, augmented inspiration, active expiration and prolongation of expiration.

Pattern of interaction (%)

<table>
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<tr>
<th></th>
<th>Synchrony</th>
<th>Augmented inspiration</th>
<th>Active expiration</th>
<th>Prolongation of expiration</th>
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</thead>
<tbody>
<tr>
<td>IPPV</td>
<td>23.9</td>
<td>4.5</td>
<td>21.6</td>
<td>50</td>
</tr>
<tr>
<td>SIMV</td>
<td>21.4</td>
<td>2.5</td>
<td>74.9</td>
<td>1.2</td>
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Active expiration was significantly more common in the SIMV group (p<0.005), whereas prolongation of expiration was significantly more common in the IPPV group (p<0.005).

Conclusions: Respiratory reflexes are provoked in term born infants by mechanical inflations. SIMV does not prevent active expiration, this may relate to trigger delay.

P4310
The influence of angiotensin-converting enzyme (ACE) genotype on the development of severe perinatal asphyxia in the neonates
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Background: The cardiovascular disturbances are the important pathways in the development of perinatal asphyxia. Study of genetic markers associated with the development of severe asphyxia in newborns is of great practical importance to develop preventive measures and child health in the future. The aim of this study was to evaluate the influence of the (ID) gene polymorphism on the development of severe perinatal asphyxia.

Methods: We conducted a case-control study of 80 cases of severe perinatal asphyxia and 110 control group. For the genotyping we used polymerase chain reaction (PCR) with further restriction fragments length polymorphism analyses. The differences in comparative groups were assessed by the Pearson chi-square test analyses and Odds Ratio determination.

Results: The incidence of the homozygous DD alleles in the neonates with severe perinatal asphyxia was 33 (41.25%), of the heterozygous ID alleles 37 (46.25%), of the homoygous II alleles 10 (12.50%). The neonates of control group had following alleles: DD - 15 (13.64%), ID - 44 (40.00%), II - 51 (46.36%).

Conclusion: DD gene polymorphism of the neonates is a risk factor for the development of perinatal asphyxia. We suggest using these genetic markers in prognosis of severe perinatal asphyxia in the neonates.

P4311
Determinants of lung function in school aged children prematurely born before 32 weeks of gestation
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Rationale: Persistent respiratory sequelae have been reported in children prema-
P4312 Infant spirometry at three months after birth in term and preterm infants

Karin Lidberg1, Paraskevi Kosma2, Gunilla Hedlin 2, Charlotte Palme-Kilander2.

Infant spirometry at three months after birth in term and preterm infants P4312 lung abnormalities are likely associated with prior BPD. lung function especially among those who did not received surfactant. Restrictive lung abnormalities are likely associated with prior BPD.

Methods: All the children born with a GA <32 weeks were included (n=444). Their respiratory outcome between 1997 and 2000 were eligible for the study. Their respiratory outcome was evaluated by a respiratory questionnaire and lung function measurements: spirometry, static lung volumes, exercise bronchial responsiveness test, pulmonary diffusing capacity DLCO. Multivariable analysis was used to evaluate the neonatal and childhood determinants of their lung function at school age. The study was approved by the Hospital Ethical Review Committee.

Results: Of the 444 eligible children, 151 (Birth Weight= 135±379 g; GA = 30±1.17 wks) were included: Age= 8±6.0±8.8 yrs, Body Weight= 28±4±6.5 kg, Height= 13±2±8cm. Bronchopulmonary dysplasia BPD occurred in 36.4% of them. At school age 60% had respiratory symptoms. Lung function abnormalities were found in 53.5% of them: obstructive abnormalities with or without distress in 41%, restrictive or mixed abnormalities in 12.5%. Exercise induced bronchial responsiveness was positive in 41%. DLCO was reduced in 15.5%. Prior BPD was associated with restrictive or mixed abnormalities (OR:6.1, CI 95%:1.1- 33.9, p=0.04). Surfactant treatment was protective from lung abnormalities (p<0.03).

Conclusions: Infants born preterm are at risk of impaired lung function especially among those who did not received surfactant. Restrictive lung abnormalities are likely associated with prior BPD.

P4313 Predicting the safety of air travel in ex-preterm infants

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Background: Hypoxia is reported in preterm neonates during medical air transfer. Predicting in-flight hypoxia in preterm infants is difficult from available data. Aims: Further investigate the response of preterm infants to flight, identify factors that may predict in-flight hypoxia and the need for in-flight oxygen.

Methods: A retrospective review of neonatal and in-flight data of all infants born <37 weeks gestation transferred between 2005-2008. In-flight oxygen was commenced if oxygen saturation decreased to <85% for >2 minutes. The impact of post-menstrual age (PMA), birth weight, duration of ventilatory support and time of flight on oxygen requirements was measured. A total of 37 infants (birth weight ≤ 1500 g, GA <32 weeks) undertaking medical air transfer between 2005-2008 were included. Oxygen requirements and in-flight hypoxia were measured during an intensive RSV season. Twenty percent of both term and preterms < one year were diagnosed with RSV. Significant correlation was found between infants with prior BPD and lower in-flight oxygen requirements. In-flight oxygen was required in 31.5% of infants. Conclusions: Very preterm (GA <32 weeks) but not moderately preterm infants did have impaired expiratory flows compared to term infants. Infection rate was significantly lower in preterms. Follow-up will be performed.

P4314 Outcome of congenital diaphragmatic hernia (CDH) in a non-ECMO unit

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Introduction: CDH management involves gentle ventilation, hypercarbia, INO & delayed surgery. ECMO use is limited & associated with greater neurodevelop- mental sequelae.

Methods: Retrospective review of all CDH neonates presenting to the Children’s Hospital at Westmead over 5 years (01/2005 to 12/2009). Infants were assessed at 1 year using the Bayley Scales of Infant and Toddler Development. Version III. Visual reward orientation audiometry was performed.

Results: Of 37 babies [M=17, referred, 5 (13%) died perioperatively, 6 lost to follow-up & 2 missed developmental review. 30/32 (93%) of the survivors were seen at 1 year and 24/32 (75%) had a neurodevelopmental assessment. Mean GA 37.9 wks (SD ±1.7) & BW 2983 gms (± 722.5). CDH diagnosed: 17 antenatal ultrasound [US] < 22 weeks of gestation, 6 later antenatal US and 14 [44%] postnatally. Median age at surgery was 7 days (range 0 to 55). 8 (21%) had an associated cardiac anomaly [4 had surgery]. Below average outcomes in 2 (8%) infants on cognitive skills & expressive language; 6 (23%) receptive language, 7 (27%) in grossmotor skills & 2 (8%) deficient in fine motor skills. No sen- sorineural hearing deficits. Neither mortality nor abnormal neurodevelopmental outcome were significantly associated with prematurity, gender, time of diagnosis, necrotizing enterocolitis or chronic lung disease.

Conclusion: Mortality rates in a tertiary level non-ECMO unit are comparable with ECMO centres and 1 year neuro-morbidty is low. The outcome from conventional strategies is comparable in the treatement of most CDH patients where ECMO is not available.

P4315 Positive end-expiratory pressure affects the value of intra-abdominal pressure in acute respiratory distress syndrome in newborn with diaphragmatic hernia

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Introduction: To examine the effects of positive end-expiratory pressure (PEEP) on intraabdominal pressure (IAP) acute respiratory distress syndrome (ARDS) in newborn with diaphragmatic hernia.

Methods: Thirty sedated and mechanically ventilated patients with ARDS admitted to a twenty-bed surgical medical ICU were included. All patients were studied with sequentially increasing PEEP (0, 6 and 12 cm H2O) during a PEEP trial. Results: Age was 5±1.7 days, weight was 1770, 44±3120 g. SAPS II was 44±14 and PaO2/FIO2 was 192±53 mmHg. The IAP was 9.2±0.5 mmHg at PEEP 0 (zero end-expiratory pressure, ZEEP), 10.8±0.8 mmHg at PEEP 6 and 13±4±0. mmHg at PEEP 12 (P < 0.05 vs PEEP). In the patients with intra-abdominal hypertension defined as IAP>12 mmHg (n= 15), IAP significantly increased from 15±3±3 mmHg at ZEEP to 20±3±3 mmHg at PEEP 12 (P < 0.01). Whereas in the patients with IAP<12 mmHg (n= 15), IAP did not significantly change from ZEEP to PEEP 12 (8±2 vs 10±3±3 mmHg). In the 13 patients in whom cardiac output was measured, increase in IAP from 0 to 12 cmH2O did not significantly change cardiac output, nor in the 8 out of 15 patients of the high IAP group. The observed effects were similar in both ALI (n=17) and ARDS (n=13) patients.

Conclusions: PEEP is a contributing factor that impacts IAP values. It seems necessary to take into account the level of PEEP whilst interpreting IAP values in patients under mechanical ventilation.
Method: In this trial, totally 88 healthy premature neonates which were just feeding and being prepared to discharge, randomly selected. The neonates first randomly placed in prone or supine position, and 30 min later SpO2 was measured during 30 minutes. Then, the infants turned from prone to supine or from supine to prone, and a repeat set of measurement was made. The collected data was analyzed by utilizing SPSS 11.5 for windows package, using Paired Sample T Test.

Results: 60.9% (53 cases) of neonates were male and 39.1% (35 cases) were female. Their mean birth weight and gestational age were 2330.9 gram (range: 1080-3400) and 34.3 weeks (range: 26-36), respectively. Their mean postnatal age was 4.2 days (range: 1-28). Mean SpO2 of those neonates during 30 min in supine position was significantly higher than prone position (94.5±3.3 Vs 91.8±5.3, P<0.001).

Conclusion: These finding suggest that prone position have not offer any advantage over the supine position in the improvement of arterial oxygenation of healthy premature neonates.

P4317
Association between severe bronchopulmonary dysplasia and serum HGF levels in premature infants during early postnatal life
Isamu Hokuto, Takeshi Arimitsu, Masayuki Miwa, Yohei Matsuzaki, Sadasivam Suresh1.

Background: Severe bronchopulmonary dysplasia (BPD) in very low birth weight infants often poses a therapeutic challenge. Therefore, it is important to make a prognosis and develop a treatment plan as early as possible. Prone position would provide us with objective data in management of CNLD infants and would help us to determine the prognosis. Cumulative frequency curves constructed with the heart rate and oxygen saturations from the data collected on the pulse oximetry channel. The respiratory rate was derived using the Labchart software. We are presenting heart rate, oxyhaemoglobin saturation and respiratory rate profile on 25 premature infants.

Methods: Using an in-house polysomnography system prospective data on respiratory effort during sleep using video camera were collected in a cohort of preterm infants under 31 weeks gestation over a 6-10 hour period continuously. We analyzed the heart rate, oxygen saturations from the data collected on the pulse oximetry channel. The respiratory rate was derived using the Labchart software. We are presenting heart rate, oxyhaemoglobin saturation and respiratory rate profile on 25 premature infants.

Results: The mean heart rate with 3.55th centiles was 155 (129-181). The mean oxyhaemoglobin saturation with 5, 95th centiles was 94.7 (85.9-98.8). The respiratory rate had significant variability between awake and sleep with the range between 34-100/min. The average respiratory rate was in the 50s for this group of infants. Cumulative frequency curves constructed with the heart rate and oxyhaemoglobin data provides us with reference ranges for this specific group of preterm infants.

Conclusion: The description of reference ranges for cardiorespiratory variables would provide us with objective data in management of CNLD infants and ascertaining home oxygen requirement.

P4319
Association between C-reactive protein levels and outcome in acute lung injury in children
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Background: Acute lung injury (ALI) is a life threatening condition affecting both children and adults. High plasma C-reactive protein (CRP) levels are associated with favorable outcome in adults with ALI, suggesting a protective physiological effect of high CRP levels. The association between CRP levels and outcome has not been studied in ALI in children.

Aim: We hypothesized that increased plasma CRP levels are associated with favorable outcome in ALI in children in terms of 28-day mortality and ventilator free days (VFD).

Methods: We performed a historical cohort study in 98 mechanically ventilated children (0-18 years) with ALI. The neonates first admitted to our unit between 2003-2010 were tested for association with mortality and VFD. Clinical parameters and ventilator settings were evaluated for possible confounding.

Results: Fourteen patients (14%) died within 28 days. The median (Q1;Q3) CRP level in non-survivors was 126 mg/L (64;187) compared to 56 mg/L (20;105) in survivors (p=0.01). For every 10 mg/L rise in CRP level, the unadjusted odds for mortality increased 8.7% (95% CI 2.1%-15.8%). Cardiovascular organ failure (COVOF) at any time was the strongest predictor for mortality (OR 30.5-95% CI 6.2-152.5). After adjustment for COVOF, for every 10 mg/L rise in CRP level, the odds for mortality increased 5.0% (95% CI -2.7%-12.6%). Increased CRP levels were not associated with an increased risk of ventilator days (p=0.14). Conclusion: We conclude that increased plasma CRP levels are not associated with favorable outcome in ALI in children. Based on our findings and existing evidence that pathophysiology in ALI in adults and children differ, we suggest future research should take these differences into consideration.

432. General thoracic surgery II

P4320
Long-term results of surgically treated non-small cell lung cancer patients depending on the protocol of preoperative N-staging
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Preoperative N-staging is one of the most important aspects in management of non-small cell lung cancer (NSCLC) patients because it has a crucial impact on prognosis of patients and helps to choose the optimal treatment plan. The aim of our study was to evaluate the long-term results of operated NSCLC patients with different preoperative N-staging protocols. Material and methods: 319 patients with resectable NSCLC were operated in our center in 2003-2008. In group 1 all patients preoperatively underwent mediastinoscopy in addition to non-invasive staging procedures (CT and PET), whereas in group 2 N-staging protocol included only CT and PET. Final TNM stage was verified based on intraoperative findings including mediastinal lymph nodes dissection. Long-term survival was assessed by Kaplan-Meier method.

Results: In group 1 significantly less unforeseen N2 were revealed during intraoperative lymph nodes dissection in comparison to group 2 (10% vs 27%, respectively, p<0.05), the rate of uncertain resections was also lower in group 1 than in group 2 (5% vs 14%, respectively, p<0.05). Analysis of long-term results showed better survival in group 1 than in group 2 (5-yr survival 61% vs 43%, respectively, p<0.05). This difference was more prominent in patients with central NSCLC (5-yr survival 65% vs 39%, respectively, p<0.01).

Conclusion: Our findings suggest that including mediastinoscopy in preoperative N-staging protocol of potentially operable NSCLC patients improves the selection of surgical candidates by excluding patients with extended disease, that results in better long-term survival of operated patients.

P4321
The evaluation of surgical results in pT0-pT1 non-small cell lung carcinoma after induction therapy
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There are good results in locally advanced non-small cell lung carcinoma (NSCLC)
surgically treated after induction therapy. We aimed to detect the role of PET-CT on recurrence, survival and preoperative assessment in surgically treated pT0N0M0 after induction therapy.

Of the patients, stage IIIb, IIB and IIIB NSCLC, undergone pulmonary resection after neoadjuvant chemotherapy or radiotherapy, pT0N0 and pT1N0. The mean age was 59.2 years, and the mean follow up was 34.8 months with mean survival time and 5-year survival rate were 90.8 months and 86.3%, 62.6 months and 53.7% (p<0.1), respectively. There were one (4%) local recurrence in T0 and eight (27.6%) local plus distant in T1 (p<0.05). 18 patients preoperatively assessed with PET-CT, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 78%, 56%, 64% and 71%. NPV in T0 and PPV in T1 were 100%. The accuracy in T0 and T1 were 56% and 78% (p<0.3).

The survival of the pT0N0 and pT1N0 NSCLC who had surgical resection after induction therapy is similar with those had resection without induction. The success of PET-CT to reveal pT0, with no live tumor cell, and pT1 preoperatively, is lower.

P4322
Inspiratory capacity is a new preoperative risk predictor in the patients with lung cancer undergoing surgical resection

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Since surgical complications implicate an enormous economic burden as a result of patient’s unexpected treatments and prolonged postoperative stay (PPS), we face an urgent need to establish preoperative pulmonary assessment to prevent pulmonary complications. We retrospectively evaluated 421 cases of the patients who underwent major lung resection in Nagoya University hospital to determine the new predictor to elucidate the risk for PPS. Chronic obstructive lung disease (COPD), irrespective of the degree of symptoms, was confirmed to be one of the most important risk factors in PPS, for patients with major lung resection. Since mounting evidences suggested that the disease severity of COPD might be strongly associated with inspiratory capacity (IC), we evaluated whether IC, measured by spirometry, could be applied to elucidate the risk for PPS in the patients. The multivariate analysis demonstrated that%IC was one of the most critical independent risk predictors for PPS. Our data suggested that%IC might be an additional risk predictor for PPS in patients undergoing major lung resection, irrespective of COPD status.

P4323
The clinical importance of preoperative inspiratory spirometry value in lung resections

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Aim: It has been aimed at investigating the relationship between the value determined with incentive spirometry (IS), which is used frequently to improve lung expansion after thoracic surgery, and clinical symptoms, pulmonary functions, and exercise capacity data; and if there is a relationship between these, discussing the importance and applicability of IS value during clinical follow up in patients with lung resection candidates.

Material-method: Twenty-two patients (6F, 16M; mean age 60.82±8.28 years) diagnosed with lung cancer (50% staged, 31.8% stageII-B) and followed with lung resection indication were assessed. The clinical characteristics and respiratory symptoms were asked. Maximal IS value (ml) was measured with IS. Pulmonary function test and 6-minute walking test were done.

Results: The mean maximal IS, FEV1%, inspiratory capacity (IC), Pimax%, Pmax%, and GMWD values were 3047±831.49ml, 76.71±15.74, 2.25±0.42, 63.53±13.67, 58.12±23.46, and 480.00±94.39 ml/min, respectively. There were effort dyspnea (31.8%), fatigue (40.9%), secretion (22.7%), cough (22.7%), and chest pain (4.5%) in patients. It was determined that maximal IS value was correlated with cough symptom (rho=0.43, p<0.05), FVC (rho=0.48, p<0.05), FEV1 (rho=0.63, p<0.001), IC (rho=0.49, p<0.05), and Pmax (rho=0.71, p<0.002) values.

Conclusion: IS value represents pulmonary functions individual of demographichal and functional characteristics of patients. Especially, due to the relationship of IS value with FEV1%, IC, and Pmax values, our results suggest that IS value may give information on the effective cough ability and thus IS value might be used during clinical follow up and routine care of patients with lung resection.

P4324
The role of PET/CT in lung cancer staging

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Routine preoperative examinations should contain PET/CT for proper staging.
Method: Our clinic’s experience in the surgery of tuberculosis is limited by the existence of an outside compartment, specialized in these types of surgeries. Between 2001–2010 we had 196 cases with postoperative diagnosis of TB. From these 196 cases we selected only 64 cases of tuberculosis, that had imagistic and clinical aspect of a lung malignant tumor.

All of these patients were admitted with a symptomaticology unlike lung TB – weight loss, fatigue, hemoptysis, no fever, no previous infections or contact with TB patients, negative bronchoscopy, sputum cultures and Quantiferon test (3 patients). The CT images showed round tumoral formations, with poor limits and pathological mediastinal lymph nodes.

Postoperative outcomes: The postoperative evolution was very good with discharge of the patient in 5 days and with medical treatment.

P4328

The comparison of exercise test in patients with lung resection candidates

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Aim: It has been aimed at investigating the consistency of the maximal cardiorespiratory exercise test (CPET), 6-minute walking test (6MWT), and stair climbing test (SCT) results with each other and discussing the applicability of these submaximal field tests in patients with lung resection surgery indication.

Material-method: The maximal cycle ergometry, 6MWT, and SCT tests were done in 22 lung cancer patients (6F, 16M) followed with lung resection surgery indication. maxVO2 value was calculated indirectly using indirect formulas for 6MWT and SCT. Peripheral oxygen saturation (SpO2) and heart rate values were recorded using pulse oximetry during test.

Results: The mean maxVO2 values were 16.07±2.70 ml/kg/min (for CPET), 24.44±4.09 ml/kg/min (for SCT), and 18.38±2.83 ml/kg/min (for 6MWT). It was determined that heart rate increased (heart rate difference; for CPET=38.20±14.67, 6MWT=20.48±9.06, SCT=48±11.56, p<0.05) and SpO2 reduced (SpO2 difference; for SCT=3.14±1.56 and 6MWT=1.48±2.52 % with p<0.05, CPET=3.95±10.30, p=0.10) after these tests. It was found that CPET maxVO2 was correlated with 6MWT and SCT maxVO2 (between CPET and SCT, r=0.59, p=0.01; between CPET and 6MWT, r=0.53, p=0.02). In addition, it was determined that there were correlations only between CPET and SCT in respect to load and work values (r=0.70, p<0.01). 6MWT can be used related to lower hemodynamical stres level in conditions the application of CPET and SCT are not possible.

P4329

The effect of neoadjuvant chemoradiotherapy on airway colonization and post operative respiratory complications in the patients undergoing esophagectomy for esophageal cancer

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Background: Different treatments are performed for esophageal cancer, but surgery is still the base of treatment. Respiratory complication is the important postoperative complications of esophageal cancer.

Methods: In this study 40 patients who were candidates for surgery of esophageal cancer were placed into two groups of with or without neoadjuvant therapy. Before surgery, they underwent bronchoscopy and bronchoalveolar lavage. The samples were analyzed for airway colonization and then the patients underwent the surgery and were postoperatively evaluated in respiratory complications and the effects of preoperative neoadjuvant therapy.

Results: M/F=23/17 and mean age was 61 years. 22 cases had cancer in the middle and 18 in the lower part of the esophagus. 25 cases had SCC and 15 had ACC. In evaluation, no organism was found in 9 cases (22.5%) and positive cases of microbial culture was found in 31 cases (77.5%). Significant relation was observed between airway positive microbial colonization and neoadjuvant therapy but no significant relation was found between neoadjuvant therapy and major respiratory complications such as pneumonia, ARDS. There was significant relation between airway positive microbial coloni zation and neoadjuvant therapy but no significant relation was found between length of hospitalization in ICU and receiving neoadjuvant therapy. Two deaths were reported due to myocardial infarction in the postoperative days. There was no death due to respiratory complications.

Conclusion: Neoadjuvant therapy can used safe and it does not cause postoperative major pulmonary complications and related mortality.

P4330

The comparison of the findings of preoperative PET-CT and surgical pathology in patients with non-squamous cell lung cancer those with and without induction therapy

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Aim: To compare the diagnostic accuracy of PET-CT in defining the pathological response to chemotherapy/radiotherapy and compare with patients operated without induction therapy in non-small cell lung carcinoma (NSCLC).

Patients, performed lung and mediastinal lymph node dissection for NSCLC, after a staging procedure with PET/CT. In first group, patients had induction therapy for a stage IIIA and IIIB disease, before PET-CT. In the second group, patients had had induction therapy for a stage IIIB disease, before PET-CT.

PET-CT has been widely used to evaluate the response to induction therapy in lung cancer. We aimed to reveal the accuracy of PET-CT in defining the pathological response to chemotherapy/radiotherapy and compare with patients operated without induction therapy in non-small cell lung carcinoma (NSCLC).

Patients, performed lung and mediastinal lymph node dissection for NSCLC, after a staging procedure with PET/CT. In the first group, patients had induction therapy for a stage IIIA and IIIB disease, before PET-CT.
second, patients had surgical resection after PET-CT evaluation. The postoperative histopathological and preoperative PET-CT findings were compared. There were 58 patients in group 1 and 59 patients in group 2. The sensitivity, positive predictive value (PPV) and accuracy of PET-CT for primary tumor were 92%, 92%, 86% in group 1 and 99%, 100%, 99% in group 2. In group 1, the specificity and negative predictive value (NPV) were 50% and 50%. For N2 disease; the sensitivity, specificity, PPV, NPV and accuracy were 44%, 88%, 58%, 80%, 76% in group 1 and 43%, 89%, 16%, 97%, 87% in group 2. The sensitivity, PPV and accuracy of primary tumor and NPV and accuracy of N2 disease were significantly lower at group 1. In patients with NSCLC those had had induction therapy, the sensitivity of PET-CT should be examined better than the patients those had not had preoperative therapy and it should not be avoided to perform invasive staging procedures. The positivity of lymph nodes in PET-CT should be confirmed by histopathology. When PET-CT findings after induction therapy is used, NPV and accuracy is lower.

P4331
A case of pulmonary sequestration behaves as cyst hydatid
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Pulmonary sequestration is an uncommon disease with non-functioning pulmonary tissue and anomalous systemic blood supply. Diagnosis depends on identification of abnormal systemic vessels. We report a case who went on thoracotomy due to cyst hydatid and the sequestration was diagnosed during the operation.

Case: A 68-year-old man complaining of a non-productive cough, stomach ache, nausea and vomiting, admitted to our clinic. He was diagnosed with hepatic cyst hydatid and was treated with surgery one year ago. Chest x-ray showed a prominence at aortic arch. Chest CT imaging was revealed a paraaortic lesion with suspicion about its density of cystic or solid which was located posteriorly.

This was taught again a hydatid cyst suitable with his medical history and an operation was planned. Left thoracotomy was performed. During the operation the lesion was detected as a sequestration. By histopathological study the lesion was confirmed to be a sequestration. In his 4th. month follow-up the patient remains asymptomatic with normal radiography results. Aberrant feeding vessels cannot always be demonstrated by conventional CT. Moreover, volumetric helical imaging allows three dimensional reconstruction of data, may be useful in the demonstration and characterization of the lesions and also showing vascular structures. Pulmonary sequestration must be in mind for differential diagnosis of pulmonary lesions especially adjacent to vascular structures.

P4332
Abcessus pulmonum: Unexpected outcome of surgical treatment; a case presentation
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This paper presents a case of 12-year-old girl, who was admitted to the pulmonology department of the Clinic for children’s illness KC Banja Luka in February 2010th year, because of the x-ray verified large tumor change in the left hemithorax. Insight into previous medical documentation, patient previously had two surgeries for a congenital deformity of the thoracolumbar spine. After admission in our department, in a differential diagnosis, we have done chest CT, GI passage, the serology of Echinococcus granulosus, ultrasonography and laboratory analyses, after which the patient was referred to the surgical treatment at the Institute for Mother and child in New Belgrade.

During the surgery a apscess cavity filled with green colored compress was found, which had been present for 2.5 years since spine surgery.

P4333
Giant mediastinal atypical carcinoid tumor
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Fifty-one years old male with shortness of breath increased by effort since one year. The patient was smoking 30 packs of cigarette per year. Inspiration sounds were decreased on the left hemithorax. Pulmonary function test results were; FEV1: 2.21 L (60%), FVC: 3.32 L (70%), PIF: 3.71 L (42%), FEV1/FVC: 68.6%. The computerized thorax tomography, showed a 155x127 mm soft tissue mass on the left anterior mediastinal region, pressing vascular structures, and heart, and causing atelectasis on the upper lobe. Incisional biopsy was taken from the mass via mediastinotomy at a different hospital; the pathology result was malignant diffuse lymphoma. PET-CT was applied for staging. 2r mediastinum hypermetabolic lymph node station, with 14.5 mm diameter was detected (SUV max: 5.4). The mass SUV max: was 8.7. Chemotherapy was applied to the patient with diagnose of lymphoma. However, due to lack of regression of mass, biopsy slides were reexamined; the diagnosis was changed to be carcinoid tumor. The mass was decided to be surgically removed by median sternotomy. The mass was quite vascular, and had tight adhesions between the lung and pericardium. The result of frozen section of the mass was reported to be atypical carcinoid tumor. The mass was removed instead of excised pericardium. The mass weight was 1300gr, size was 17.5x15x9.5 cm. No tumor was detected within surgical margins. Chromogranin, Synaptotizin, CK, and CD 56 was positive at the immunohistochemical panel. Microscopic findings were confirmed atypical carcinoid tumor. In conclusion, mediastinal carcinoid tumors are very rare. Their origin of tumor is difficult to determine. Surgery is the current treatment method.

P4334
Robotic-assisted thymectomy by da Vinci II versus sternotomy in the surgical treatment of non thymomatous myasthenia gravis
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Introduction: Thymectomy in myasthenia gravis is controversial. Remission rate 5 years after surgery in literature varies from 13 to 51%. Sternotomy is the standard technique, not acceptable because of possible complications. Our objective was to demonstrate that the robot-assisted technique is at least as efficient and leaves less scars than sternotomy.

Methods: We retrospectively reviewed data of 30 patients with myasthenia gravis operated on in our center from January 1998 to December 2009. Two groups were formed: group 1 corresponding to patients who received a sternotomy, group 2 patients the robotic-assisted technique. Hospital stay, pain on D1, 1 year improve-

Results: We identified 13 women and 7 men. The mean age was 31 years old. The mean delay before surgery was 24.8 m. Group 1 consisted of 15 patients, group 2 of 5. Complete remission rate at 1 year was 5%. Surgery decreased the frequency of relapses equally in the 2 groups. Hospitalization stay and pain on D1 in group 2 were significantly lower than those in group 1 (p<0.04, p<0.001). Postoperative improvement was not significantly different between the 2 groups.

Conclusion: Results at 1 year of the 2 techniques are fully comparable. Robot provides additional benefits: minimal esthetic sequelae, less parietal morbidity, shorter hospital stays. Our complete remission rate, lower than those in the liter-

ate, must take into account the early nature of these results. The surgical robot appears to be a promising technique and should facilitate the early management of these patients.

P4335
Impact of neoadjuvant therapy on tumor resectability and survival of patients with locally advanced non-small cell lung cancer
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Background and aim: Surgery is the treatment of choice in early stage non small
cell lung cancer (NSCLC). It is also used in some cases of locally advanced tumors, but with a low cure rate. Therefore, preoperative treatment is seeking to improve survival in these patients. The aim of this study was to evaluate tumor resectability and survival in patients with locally advanced stage (IIA and IIIB) NSCLC treated with chemotherapy (CT) and chemoradiation therapy (CT-RT) neoadjuvant

Methods: This was a retrospective study that evaluated patients with locally advanced NSCLC in a university hospital during 2000-2006, that received induction therapy. The collected variables were anthropometric values, histology, stage of the tumor, neoadjuvant treatment and therapeutic response. Kaplan-Meier curve was used to evaluate survival and analysis of variance to compare values among groups.

Results: 32 patients were included; 9 subjects (28%) were diagnosed with stage IIA and 23 (72%) stage IIIB, being the IIIB the most common indication for induction therapy. All patients were treated with CT, showing a treatment response in 80% of cases and only 7 were also required RT. Resection was indicated in 31 patients and only in 6 subjects exploratory thoracotomy was performed, seeing a downstaging in 46.9% of all the cases. Overall 5 year survival was 27.8% with a median of 52.9 months (95% CI 38.1-67.6). This survival is dependent on the response to neoadjuvant.

Conclusions: Neoadjuvant cancer reduces tumor size resulting in a downstaging and improving the resectability of locally advanced NSCLC. It could be a viable therapeutic option to improve survival of these patients.

P4336
Surgical treatment of combination of tuberculosis and pulmonary echinococcosis
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Results of surgical treatment of combination of TB and pulmonary echinococcosis were studied in 19 patients (males-11, females - 8) in ages 7-47 years old. Fibrous-cavernous TB was diagnosed in 4, pulmonary tuberculosis in 8, focal in 3, TB of intrathoracic lymph nodes in 1. In 9 patients echinococcus cysts located within the zone of tubercular affect, in 10 in other lobes of lung, in 9 on the left. Cyst dimensions were 2 to 9 cm in diameter. In 4 with location of echinococcus cyst in the zone of tubercular affect were operated - segmental resection was performed in 1, lobectomy in 2, lobectomy and thoracotomy in 1. In 7 who had TB and echinococcus cyst in different lobes of lung, single-stage segmental resection and echinococcectomy was performed in 5, lobectomy and echinococcectomy in 1, combined resection and echinococcectomy in 1. After effective chemotherapy and repair of pulmonary destruction, an organ-saving operation – echinococcectomy was performed in 8 patients with firstly diagnosed fibrous-cavernous tuberculosis (1), infiltrative (3), focal (3), intrathoracic lymph node tuberculosis (1) and pulmonary TB. Good clinical effect was achieved in all 19 observed patients.

Conclusion: Partial resections are surgical indication at TB and echinococcosis both located in one lobe of lung, in different lung lobes – partial resection on account of TB and echinococcosis are the surgical indication. At firstly found TB and echinococcosis cyst, an organ-saving operation – echinococcectomy is necessary after effective chemotherapy and repair of pulmonary destruction. These operations are highly effective and heal patients from TB and pulmonary echinococcosis.

P4337
Pulmonary hydatic cyst: Analysis of 1024 cases
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Objective: Pulmonary hydatic cyst is a parasitic disease and health care problem in developing countries. In this study we evaluated treatment outcomes of pulmonary hydatid disease in our Department.

Methods: Patients admitted with pulmonary hydatid cyst from 1980 to 2010 were analyzed in this study and demographic data, size and number of cysts, diagnostic methods, type of operations, outcomes and rate of recurrence were statistically analyzed.

Results: In 1024 patients, mean age was (30.6 ±16.1) years and M/F=1.09. The most common symptom was cough (55.1%). Only 1% was asymptomatic. 53.8% had right side involvement, 40% had left side involvement and 6.2% had bilateral disease. Inferior lobe was the most common involved lobe. The cyst was intact in 53% (52.6%) patients and other, were complicated or perforated. The most common surgical technique was removing the cyst membrane without resection of pericyst and closure of orifice of airways (67.2%). The cyst was enucleated in 21.2% and par enchyinal resection was performed in 8.4% of patients. The cyst was intact in 539 (52.6%) patients and other, were complicated or perforated. The most common surgical technique was removing the cyst membrane without manipulation of pericyst and closure of small airways. Pulmonary resection should be reserved for complicated forms of disease.

Conclusion: The best treatment for pulmonary hydatic cyst disease is surgery with low mortality and morbidity. The most common and acceptable treatment is extraction of cyst membrane without manipulation of pericyst and closure of small airways. Pulmonary resection should be reserved for complicated forms of disease.

P4338
Surgery of relapsed hydatid disease of lungs
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The surgical treatment of hydatid disease of lungs is unique and the most radical, however and after operations the development of relapses is possible. On the data of the literature the relapse of hydatid disease after surgical treatment does not tend to decrease and changes from 3% up to 54%.

In the department of surgery of lungs and mediastinum Republican Specialized Center of Surgery named after acad. V.Valiyev from 1975 to 2009 years there were on treatment 2600 patients with hydatid disease of lungs. From 2600 operated patients concerning the various forms of hydatid disease of lungs relapse of disease from 1 to 7 years we observed in 160 (6.5%) patients. From them men - 93 (58%), women - 67 - (41.9%). The age of the patients varied from 10 to 70 years. From 160 patients 130 (81.25%) underwent operations, not operated 30 (18.7%) - the reason was disseminated process, wide distribution of hydatid cysts. 152 (95%) patients underwent performed organizing operation, 8 (5%) patients underwent resection.

In the postoperative period albedozam was administered in a dose 10-12 mg/kg/day, quantity of courses depended on the form of a defect.

P4339
Transthoracic approach in adult Morgagni hernias: 30 years experience
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Background: Morgagni hernia is a rare congenital disorder. Numerous approaches have been described and, particularly the significance of laparotomy has been emphasized as an important operative technique.

Aims and objectives: To present our experience on adult patients with Morgagni hernia operated on via transthoracic approach in our department.

Methods: Between 1980 and 2010, 33 patients with Morgagni hernia were operated. Twenty-two of them were male and 11 were female. Their age ranged from 17 to 77 years (mean 53.17). There were 17 females. Chest x-rays, thorax computed tomography, magnetic resonance imaging, barium enema, and pneumoperitoneum were used as diagnostic utilities.

Thoracotomy was performed in all cases. In only one case, laparotomy was applied in addition to thoracotomy.

Results: Twenty-five hernias (76%) were right-sided and eight (24%) were left-sided. Hernia sac was present in all cases. Exploration revealed only omentum in women (n=11 - 67.5%). The age of the patients varied from 10 to 67 years (mean 53.17). There were three patients (9%), stomach, colon and omentum in two patients (6%), only small bowel in two patients (6%), stomach, and omentum in one patient (3%), and only stomach in one patient (3%). The reason for the hernia formation was no complications and no mortalities.

There was no recurrence or symptoms related to the operation. The mean follow-up was 11 years.

Conclusions: We advocate transthoracic approach for surgical exposure as it provides wide exposure and repair of Morgagni hernia.

P4340
Delayed epidemic peak of pandemic influenza A (H1N1-2009) among hospital workers: The association between hand hygiene behavior and the consumption of disposable hand paper
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Introduction: Health care workers should wash their hand in the season of influenza virus infection. Since the frequent hand-washing behavior would result in the increased consumption in the disposable hand paper, the association firstly between the campaign by infection control team (ICT) and the consumption of disposable hand papers was investigated, and, then, that between the consumption and the number of patients with influenza-like illness (ILI) in the season of pandemic influenza H1N1-pnd 2009.

Result & discussion: ICT had given 6 alerting lectures and delivered 5 notices to all of the hospital workers prior to the pandemic to encourage them for the frequent hand hygiene. As a probable result, the consumption of paper towel increased by 43% for three months from September to November. In parallel with the epidemiologic trend of the whole Japan, among 8,324 outpatients in total who were diagnosed with ILI in the observed period, 33% of them visited our hospital at October, forming a peak through the term. On the other hand, interestingly speaking, 208 hospital staffs suffered ILI in the season, while they formed a small peak at December, and significantly later than that of the outpatient in October (P<0.001).

433. Influenza A (H1N1): lessons after the epidemic
P4341

**Pneumonia and pandemic influenza virus A (H1N1)/09. Immediate and remote respiratory effects**

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**Aim:** To assess the clinical presentation, treatment outcomes and long-term results for patients with community acquired pneumonia (CAP) during a Virus A (H1N1)/09 in 2009-2010

**Methods:** The study includes 250 cases of CAP, which developed in patients infected with H1N1/09 of them men 54.8%. The average age of 45.0 years. Medication consisted of oseltamivir dose to oral 75-150 mg twice daily and cephalosporins III + macrolides II or respiratory fluoroquinolones. After the end of appropriate treatment based on changes in the lungs according to high resolution CT (HRCT) was administered N-acetylcysteine (NAC) dose to oral 600 mg twice daily (n=91) for 92.0% (95% CI 86.2-97.7) days. Assessments included clinical symptoms, co-morbidity, SpO2, laboratory tests, and X-raying.

**Results:** The median period of hospitalization was 15.2 days. The median SpO2 during hospitalization was 97.9%. After hospital treatment 94.2% 76.5% of patients had a 2-side lung. The fatality rate was 10.4%. SYRS was diagnosed in 49.6% of patients (fatality rate was 1.6%), severe sepsis and septic shock in 27.6% of patients (fatality rate was 34.8%). Fatality rate in patients with obesity was 30.0% with COPD 16.3%. X-ray changes after hospitalization were 82.4% of patients, of whom 56.6% - infiltration of the lung tissue. After treatment with NAC X-ray of the variation persisted in 57% of patients, of whom 7.0% infiltration of lung tissue and 36.9% - the picture “mule”

**Conclusion:** CAP during an epidemiologic outbreak of. Influenza A/H1N1/09 characterized by severe, requires intensive care and long-term observation.

P4342

**H1N1 influenza – A second wave? Experience from the large teaching hospital in the UK**

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**Introduction:** The new H1N1 influenza (pH1N1) virus largely ran its course by August 2010 as the WHO declared the pandemic to be over, fortunately without causing as much devastation as provisionally predicted. However the impact of the outbreak on our healthcare system was considerable. In the post-pandemic period, although the rates of pH1N1 have been reported to be lower the risk of severe illness caused by pH1N1 remains. This epidemiological study reflects our experience in a large teaching hospital of the significant morbidity and mortality associated with admission to hospital with H1N1 influenza during the recent the season.

**Methods:** We retrospectively analysed the electronic records for all patients admitted with H1N1 infection between 1st November 2010 and 1st January 2011 to identify patient demographics, length of stay, co-morbidity and outcome.

**Results:** 280 patients were identified (mean age 39.5) with an average length of stay of 6.35 days; mortality 4%. A third had no co-morbidities. Overall 37 (13.2%) of patients required respiratory support (18 intubated, 19 NIV/CPAP). This is comparable to the pandemic of 2009 when 10–30% of laboratory confirmed cases had TLoC≤85%, 42% were hypoxic after 6 Minute Walking Test (6MWT).

**Conclusion:** After a severe pandemic due to H1N1 influenza, one third of the patients had the LF and HRQoL affected. Patients who required MV had greater impairment in LF and in the HRQoL.

P4345

**RNA interference against influenza A (H1N1) virus**

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**Aim:** To describe early abnormalities in LF and QoL of patients with influenza A (H1N1)/09 in 2009.

**Methods:** Clinical characteristics, and laboratory samples at the arrival to the emergency room were recorded in 135 patients with H1N1 influenza moderate to severe pneumonia. LF and health related QoL questionnaires (HRQoL) were measured after two months of hospitalization. All subjects had no clinical antecedent of respiratory disability.

**Results:** Mean age was 40±11 years, 64% were males. Kyri Index (KI) was 24±5.5, the APACHE score was 11±5.3, 30% required mechanical ventilation (MV). 35% had FEV1/FVC <0.70 or >0.85, 31% had PaO2 <60 mmHg; 33% had TLoC≤85%, 42% were hypoxic after 6 Minute Walking Test (6MWT). Four Short-Form 36 (SF-36) domains had ≤70 score and 40% had a Saint George Respiratory Questionnaire (SGRQ) >30 points; 36% had in the SF-36 physical limitation domain (PLSF-36) a score ≤50; Those with MV had more affection in LF in comparison with those without MV (PVC 96±16 vs 104±16; p<0.05). FEV1/FVC 84±6 vs 81±7; TLoC≤50±22 vs 66±21; 6MWT 431±127 vs 508±97 meters; p<0.05. The HRQoL was worse in MV vs no MV [PLSF-36 37.5 (0.81) vs 100 (50-100), p<0.05]. KL correlated with TLoC≤50 (r=0.30), P=0.003; CURB-65 with TLoC≤50 (r=0.20), p<0.04. PLSF-36 correlated with TLoC≤50 (r=0.42), KI (r=0.27) and TLoC≤50 (r=0.21).

**Conclusion:** After a severe pneumonia due to H1N1 influenza, one third of the patients had the LF and HRQoL affected. Patients who required MV had greater impairment in LF and in the HRQoL.
P4346 Clinical features and outcomes of patients hospitalized with influenza A virus (H1N1) infection in a hospital in the south of Spain

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Aim: To describe the characteristics and outcomes of patients hospitalized H1N1 influenza infection.

Methods: Retrospective analysis of the medical records of patients hospitalized with H1N1 influenza in our hospital (August 09/April10). All patients underwent nasopharyngeal PCR swab for H1N1. Results are expressed as mean ± standard deviation for quantitative variables.

Results: 93 patients (18.34%) were positive for influenza A virus. The clinical features, risk factors and outcomes are available in the tables.

Table 1: Risk Factors

<table>
<thead>
<tr>
<th>Any risk factor</th>
<th>Pregnant women</th>
<th>Smokers</th>
<th>Cancer</th>
<th>Chronic lung disease</th>
<th>Obesity</th>
<th>Diabetes</th>
<th>HIV</th>
<th>Asthmatic history</th>
<th>Immunosuppressive therapy</th>
<th>Heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (71%)</td>
<td>8 (8.6%)</td>
<td>24 (25.8%)</td>
<td>3 (3.4%)</td>
<td>35 (37.6%)</td>
<td>22 (23.7%)</td>
<td>16 (17.2%)</td>
<td>2 (2.2%)</td>
<td>17 (18.3%)</td>
<td>5 (5.4%)</td>
<td>16 (17.2%)</td>
</tr>
</tbody>
</table>

Table 2: Clinical features and outcomes

<table>
<thead>
<tr>
<th>Age</th>
<th>Male / Female</th>
<th>Average ICU stay</th>
<th>Intubation</th>
<th>Average Mechanical Ventilation</th>
<th>Average hospital stay</th>
<th>Average ICU admission</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.67 ± 20.7</td>
<td>43 / 50</td>
<td>15.9 ± 11.1 days</td>
<td>10 ± 8.8%</td>
<td>16 ± 15.3 days</td>
<td>12 (12.9%)</td>
<td>4 (4.3%)</td>
<td></td>
</tr>
</tbody>
</table>

The presenting symptoms were fever (89.2%), cough (92%), dyspnea (65.5%), digestive problems (26.9%), myalgia and headache (53%). 52.2% had community acquired pneumonia on admission. Major complications during hospitalization were (15.6%): respiratory insufficiency (50%), Acute Respiratory Distress Syndrome (9%), pneumonia (3.3%), pleural effusion (1.1%) and multi-system organ failure (3.4%).

Conclusions: Patients hospitalized for H1N1 infection are mainly middle-aged. Pneumonia and/or decompensate co-morbidities were the main causes of hospitalization. The most common risk factor was the chronic lung disease.

P4347 The changing distribution pattern of H1N1 infection in adults in 2010-2011

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Background: Since the emergence of H1N1 influenza in 2009, the World Health Organization (WHO) identified that patients with co-morbidities, pregnant women, and those over 65 years are at high risk of severe complications.

Aims and objectives: To characterise adult patients admitted with H1N1, particularly those with pneumonia, or those requiring intensive care unit (ICU) admission.

Methods: H1N1 positive inpatients from December 2010 to January 2011 were studied using electronic patient records, medical notes and the PACS system. Co-morbidities are recognized as per WHO guidance.

Results: In total 76 patients were admitted with H1N1, 35 patients with H1N1 had radiological evidence of consolidation, 8 were associated with the H1N1 winter outbreak of 2010-2011, and the impact on clinical course.

Conclusions: H1N1: The co-infection conundrum

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Background: Bacterial co-infection is known to increase the severity of H1N1 influenza. Past pandemics have been associated with Staphylococcus aureus which can lead to severe infection. Increasingly co-infection with Streptococcus pneumoniae has been recognised with H1N1 influenza.

Aims: To evaluate the causative organism’s associated with co-infection; in association with the H1N1 winter outbreak of 2010-2011, and the impact on clinical course.

Method: A patient cohort with proven H1N1 influenza admitted between December 2010 and January 2011 were retrospectively studied, using electronic patient records and paper medical notes. Bacterial co-infection was identified by positive result from blood, respiratory secretion or pneumococcal urinary antigen test.

Results: Out of a total 76 H1N1 positive cases blood, respiratory sample and urinary antigen testing was performed in 53 patients. Co-infection was detected in 12 of 53.

P4349 Platelets and influenza A (H1N1)

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Introduction: In January 2011 we had two patients with Influenza A(H1N1) in our clinic and both of them had moderate thrombocytopenia. Therefore we decided to observe the abnormalities of thrombocytes during Influenza A(H1N1) pandemic.

Materials and methods: Retrospective study based on medical records of 21 consecutive patients admitted in our clinic (November 2009- January 2010) for pandemic A(H1N1) and respiratory failure. Twelve patients had underlying diseases: obesity (6), diabetes mellitus (3), BP (2), asthma (3), HTA (11), TBC-SIDA (1). There were seven exitus (30%).

Results: From 21 patients (11 female) nine (42.95%) patients had thrombocytopenia. In four of this nine cases (44.4%) thrombocytopenia was accompanied by low mean platelet volume (under 7 fl). The degree of thrombocytopenia was moderate (96000-110000/microl.), and it was correlated significantly with the degree of inflammation measured by the serum C-reactive protein concentration. Also, all these patients had elevated levels of LDH and serum transaminases.

Conclusions: Influenza A(H1N1) virus can induce a lower number of platelets. This virus can impair even platelets functions: in four cases thrombocytopenia coupled with low mean platelet volume (MPV), elongated APTT and elevated levels of D-dimers, which can suggest an impact of Influenza A(H1N1) on coagulation. The platelet count can evaluate and monitor the efficiency of treatment: the thrombocytes count is the first parameter that returns to its normal levels in cases with a good evolution.

The evolution of number and mean volume of thrombocytes can be predictors of evolution of infection with Influenza A(H1N1): from seven exitus three patients had thrombopenia with low MPV.

P4350 General characteristics of pneumonia cases developed during H1N1 epidemic in Turkey and prognostic factors

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Aim-method: This multicentric study took place in Turkey to evaluate general characteristics of pneumonia developed during H1N1 epidemic between Nov-2009
The H1N1 influenza pandemic and pneumonia in Iceland 2009-2010: A one year follow up study.
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Background: The influenza A (H1N1) pandemic in 2009 caused in a minority of infected severe pneumonia and respiratory failure.

Aims: To characterise patients admitted to our hospital with H1N1 influenza A infection and pneumonia at one year follow up.

Methods: Patients with positive tests for H1N1 influenza and pneumonia with fulkile illness and no other known pathogen were contacted 6 and 12 months after admission. Clinical examination with specific questionnaires (SF-36, HAD and St. George questionnaires) along with spirometry were performed to collect information on pulmonary symptoms, pulmonary status and health-related quality of life. Radiographs were reviewed and repeated when abnormal.

Results: 84 patients (42 women and 42 men) were admitted with influenza associated pneumonia. The mean age was 51 years and mean BMI 33. The mean total hospital stay was 10 days. 50% of the patients required high-flow oxygen, and 26% of the patients were admitted to the Intensive Care Unit. There was one death during the initial hospitalisation due to sequelea from H1N1. 44 patients participated in the follow up study. After 6 months only 3 patients had residual radiographic changes. Pulmonary function after 6 months in the patients admitted to the ICU were: FVC 102%, FEV1 100%, TLC 85% and DCO 81% of predicted. Currently we are evaluating patients at the 1 year follow up including health-related quality of life.

Conclusions: The H1N1 pandemic in Iceland resulted in pneumonia with considerable morbidity. Our preliminary results indicate that the physiological and radiographic sequelae are minor.

P4354
Pneumonia in H1N1 influenza infection
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Introduction: As we entered the post 2009 H1N1 influenza pandemic period, the Centres for Disease Control and Prevention reported that a third of H1N1 deaths were attributed to co-infection with common pneumonia causing bacteria. We performed a study of all the patients admitted to a large teaching hospital during the most recent flu season in 2010/11 with the aim of looking at radiological diagnosis of pneumonia and its relation to morbidity and mortality.

Methods: We retrospectively analysed the electronic records and radiology for all patients admitted with H1N1 infection between 1st November 2010 and 31st January 2011. Complications and respiratory support (invasive or non-invasive) were used as markers of morbidity.

Results: 280 (mean age 39.5) patients had laboratory confirmed H1N1 infection. 96 (34.3%; mean age 44.5) had radiological pneumonia (48 unilateral, 48 bilateral); mortality 8.3% (37.5%) had no co-morbidities. Of all those that died with H1N1 8/37 (21.6%) had pneumonia. 11.5% had complications: 5 effusion/empyemas, 4 ARDS and 2 pneumothorax. 31.3% required respiratory support. 96 (34.3%; mean age 44.5) had radiological pneumonia (48 unilateral, 48 bilateral); mortality 8.3% (37.5%) had no co-morbidities. Of all those that died with H1N1 8/37 (21.6%) had pneumonia. 11.5% had complications; 5 effusion/empyemas, 4 ARDS and 2 pneumothorax. 31.3% required respiratory support. All those that had both bilateral pneumonia and complications (n=8) required respiratory support of which 3 died. 26% had positive sputum cultures-most common pathogens being haemophillus influenza, streptococcus pneumonia, klebsiella and candida. 50% of those requiring respiratory support had positive sputum cultures.

Conclusion: Pneumonia in H1N1 infection is common. Bilateral pneumonia is a risk factor for the need for respiratory support and death. Development of respiratory complications confers further risk of morbidity.

P4355
A study to analyse the clinical profile and outcome of hospitalised patients with H1N1 and the factors influencing the outcome
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This was an observational study conducted in Institute of chest diseases, Calicut medical college,India between August 2009 and August 2010. All patients whose
likely to have two or more lung zones involved (p <0.005). 11 (35.5%) patients had pleural thickening or effusion.

Conclusion: In patients with the novel swine flu the most common radiographic abnormality observed in our center was consolidation in the lower lung zones. Patients admitted to ICU were more likely to have two or more lung zones involved.
Introduction: Oxidative stress and reactive oxygen species (ROS) are implicated in influenza A virus-induced lung inflammation and damage. Current therapies primarily target viral infection and replication, with little attention directed at the host immune response. The antioxidant enzyme glutathione peroxidase-1 (GPx-1) has a protective role against various diseases involving ROS.

Aim: To study the role of GPx-1 in influenza A virus-induced lung disease.

Methods: Male WT (C57BL/6) and GPx-1 -/- mice were infected with 1 × 10^6 PFU of HKx31 (H3N2) influenza A virus. Viral titre, BALF and lung inflammation, body weight, pro-inflammatory chemokine (MIP-1α, MIP-2, KC) and protease (MMP-9) expression were assessed 3 and 7 days post infection.

Results: WT mice infected with HKx31 had significantly more BALF total cells and neutrophils than infected WT mice (P < 0.05). Viral titre was significantly reduced in GPx-1 -/- mice at day 3 compared to WT mice (P < 0.05). Infected GPx-1 -/- mice lost similar amounts of weight to infected WT mice. Gene expression analysis revealed that GPx-1 -/- mice had more whole lung MIP-1α, KC and MIP-2 than WT mice at day 3. Infected GPx-1 -/- mice had more active MMP-9 protease in BALF and greater peribronchial inflammation and bronchial inflammatory cell exudates than infected WT mice.

Conclusions: These data indicate that GPx-1 reduces some aspects of influenza A virus-induced lung inflammation, which may improve overall outcomes of influenza infection.

P4354
Biomarker profiles of BALF in ALI/ARDS due to pandemic (H1N1) 2009 influenza
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Background: The outbreak of the 2009 pandemic influenza A (H1N1) virus was identified as a Pandemic. However, the clinical and epidemiologic characteristics of the novel influenza were not sufficiently elucidated.

Methods: Patients who were hospitalized because of the novel influenza infection were enrolled in the study between August 2009 and December 2009 at Shinshu University Hospital. Furthermore, the patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) due to influenza A infection were collected. The patients' condition, laboratory data, the respiratory management, and oxygenation were analyzed. Bronchoalveolar lavage (BAL) was performed on admission.

Results: Nine patients were hospitalized and treated with anti-viral therapy such as oseltamivir. Five of 9 patients showed ALI/ARDS. Three of the 5 patients were intubated and non-intubated patients. Only one patient died in the intensive care unit because of the refractory hypoxemia due to the deterioration of a co-infection. BAL was performed in 3 patients and all of them showed alveolar hemorrhage. The patients' condition, laboratory data, the respiratory management, and oxygenation were analyzed. Bronchoalveolar lavage (BAL) was performed on admission.

Conclusion: This study showed lung injury due to 2009 pandemic influenza A (H1N1) virus was formed by the direct ALI/ARDS without a cytokine storm. This was significant difference between the intubated and non-intubated patients.

P4355
Glutathione peroxidase-1 as a therapeutic target in influenza A virus-induced lung disease
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Objective: To evaluate the sequelae of viral (H1N1) pneumonia at 3,6,12 months follow-up.

Methods: We evaluated 22 survivors of the influenza A (H1N1) virus pneumonia at 3, 6, and 12 months after discharge. At each visit, the patient was interviewed; underwent a physical examination, pulmonary-function testing, chest radiography, 6MWT and a quality-of-life evaluation.

Results: At discharge all patients had abnormal chest radiographs, DLCO values below 80% of predicted (50.7 ±21.6%) and 6MW distance was shorter than in normal values in the same age groups (498.5 ±54.2m).

Conclusion: There was significant difference between the intubated and non-intubated patients revealed a continuing significant difference in lung diffusing capacity at 3, 6, and 12 months (DLCO 62.1 ±8.3% vs 85.7 ±3.2% p=0.01 DLCO 67.3 ±5.2% vs 89.0 ±2.2% p=0.01 DLCO 67.9 ±4.7% vs 92.2 ±1.5% p=0.01 respectively).

P4356
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Conclusion: This study showed lung injury due to 2009 pandemic influenza A (H1N1) virus was formed by the direct ALI/ARDS without a cytokine storm. This was significant difference between the intubated and non-intubated patients.
434. Challenges in tuberculosis control


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Introduction: Diagnosing latent tuberculosis (TBIL) in patients with rheumatoid arthritis (RA) has become more important with the introduction of the use of anti-TNF alpha agents and the appearance of active tuberculosis in these patients.

The tuberculin skin test (TST), has limited value when used in patient with RA. New tests based in the production and release of IFN-gamma have been studied but their role has not been well established for this specific group of patients.

Objectives: Comparing the diagnosis of TBIL in a group of patients with RA by using tuberculin skin test, TSPOT-TB and by means of tomography findings compatible with TBIL.

Methods: A clinical-epidemiological evaluation, use of TST, TSPOT-TB and high-resolution computed tomography (TCAR) in a group of patients with RA in University Hospital of Goiás, Brazil.

Results: The response to the TST was smaller in patients with RA (13.5%), relative to the response expected from the general population. The TSPOT-TB identified a higher number of patients with TBIL, relative to the TST (36.8%). TCAR presented changes which were compatible with TBIL in 52.9% of the patients included in the study, and among the eight of the eleven patients with TST and TCAR identified as negative.

Conclusions: In isolation, TST is an insufficient test to diagnose TBIL. A higher number of positive results were obtained with TSPOT TB, relative to TST, but it was negative in a large percentage of patients with tomography findings consistent with TBIL. The TCAR test is easily performed in most of the large centers and should be incorporated into the diagnostic strategy for TBIL in patients with RA.

P4361 Use of econometric selection models to describe non-completion of treatment for latent tuberculosis infection (LTBI) among the Egyptian and Somali immigrant populations

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Tuberculosis (TB) is a global health concern, with 2 million deaths each year. Treating immigrants with latent tuberculosis infection (LTBI) has become a priority in the U.S., as active TB rates decline. The study investigates treatment adherence for LTBI via econometric selection models for two reasons: only the healthiest of immigrants migrate and LTBI returns to migration. Therefore, Heckman’s sample selection model was used to estimate the demand among non-immigrants for TB prevention to be high in endemic countries. We never realize this demand because these individuals do not migrate. We expect the demand among non-immigrants for TB prevention to be high in endemic countries. For individuals who did (not) immigrate, we assume that the risk of developing active TB disease is lower (higher) than the risk of developing a latent TB infection. For individuals who did in a way that increased complete treatment vary systematically from those who did in a way that increased their future probability of disease activation.

After correcting for the biases of the “healthy immigrant effect” and the self-selection into treatment, we assume that the risk of developing active TB disease is lower than the risk of developing a latent TB infection. We expect the demand among non-immigrants for TB prevention to be high in endemic countries. We never realize this demand because these individuals do not migrate. Therefore, Heckman’s sample selection model was used to estimate returns to migration.

Initiation and duration of treatment is significantly associated with length of time in the United States (p<.05). Among immigrants who did not complete treatment, HbA1c/vitamin D levels were significantly greater/lesser than those who did complete treatment (p<.05).

In an urban city, a decision was taken in 2004 to modify tuberculosis (TB) contacts screening strategy from targeting only close contacts identified by interview with the index case (the national policy) to a screening strategy involving home and work visit.

The present study compares TB contact-tracing during the periods 2001 to 2003 and 2004 to 2006 trying to capture how the new contact tracing strategy addressed the three main questions: (i) Does this strategy increase TB screening compliance? (ii) Does it identify more at-risk contacts? (iii) Does it result in more TB cases being prevented?

Home and work visit allowed to identify more at risk contacts (8.4/4.04 index case) than the interview (2.5/4.04 index case) to improve compliance (87.3% of the identified contacts were screened, compared to 67.6%). More cases of active TB and LTBI cases were detected (1.4/4 index case compared with 0.75/4 index case) and prevented more TB cases in the future.

The newly implemented contact-screening program with home and work place evaluation of active TB patients, improved compliance to screening procedures, identified more at-risk contacts and should allow us to prevent more TB cases in the future.

P4363 Tuberculosis in prisons of Republic of Macedonia from 2005-2010

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Introduction: Prison’s population (yearly approximately 2600 prisoners) is group with higher risk of tuberculosis (TB) due to fullness of prisons, bad living conditions and inadequate medical care. Total population’s notification rate decreases continuously but the rate of TB cases in prisons is still high (384/2005, 2/2006, 15/2007, 230/2008, 307/2009 and 384/2010). Aim of this survey is to prove the situation with TB in prisons in Macedonia.

Material: Data for this study were taken from the Central TB Registry. The forms of TB, previous treatment, bacteriological confirmation and treatment outcome between 36 prisoners (period 2005-2010) have been analysed.

Results: In the period 2005-2010, 36 cases of TB were registered, 91, 6% male and 4, 4% female. The pulmonary TB was identified at 83, 3%, extra pulmonary TB at 16, 7% cases. From all cases, 83, 3% were new and 16, 7% previously treated. Bacteriological confirmation of pulmonary TB with direct microscopy identified at 43,3% and bacteriological confirmation of culture at 63,3% cases. The drug sensitivity test demonstrated multi drug resistance in 2,7% cases. Treatment outcomes from 2005-2009 were following: successful treated 80, 9%, dead 3, 8%, default treatment 11, 5% and 3, 8% lost from evidence. Drug addiction is finding in 41, 6% prisoners with TB.

Conclusion: Rate of TB in prisons in Macedonia is higher than in total population. Among TB cases in prisons percentage of bacteriological confirmation is low. Appearance of multi drug resistant form of tuberculosis is bad prognostic sign.

P4364 Two major problems in TB patients today: MDR and the abandoned therapy

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In the WHO strategy, “stop TB” is the ultimate goal in the fight against this extended infectious disease. However, despite this ambitious purpose and the tools developed in this matter, the problems may occur. Aims: In this paper, the authors proposed to emphasize the latest and striking observations on difficulties encountered in TB treatment, in a pneumology department.

Methods: We observed the TB cases admitted in our service in 2010 compared with 2009 and noted the chronics, relapse cases. We noted why these patients couldn’t rich to a proper end of their treatment and be cured. Equally, we were interested in number of MDR cases admitted in both years, comparative.

Results: All TB patients evaluated in 2010 were 456. From these, 255 were chronics, developing at least a third treatment (by failed or abandoned treatment). From these ones, 12 patients were with secondary MDR (5 of them with additional resistance to SM or EMB). Besides, we had 2 patients with XDR. In 2009 we had 468 TB patients, from which 214 were chronics, 165 abandoning their schedule and coming to hospital in 2010. In 2009 we noted just 5 patients with MDR. It is worth noting the lack of secondary aminoglicosides like Kanamicine and Amikacine and the impossibility of admitting all these patients in the unique service of MDR in town.

Conclusions: We are worried about the increase of number of cases with treatment abandon and the MDR cases. There is an important number of patients who cannot be compelled to follow the treatment when they leave the hospital (because of different reasons: social, tolerance, first treatment failed). Isolation of MDR cases from other TB patients in the same hospital seems difficult.

P4365 Profile of TB deaths in Romania during 2007-2009

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Introduction: Even TB is a curable disease from several decades, it’s estimated that it is still killing over 1.7 million people early worldwide. The TB mortality rate decreased in Romania since 2003, in parallel with the decrease of notification...
rate, but the proportion of deaths from all reported TB cases is keeping more than 6.5%.

Aims and objectives: To study the profile of TB deaths in Romania during 2007–2009 on the demographics data of the deceased persons, their associated diseases and depending on the bacteriological confirmation of pulmonary TB case.

Methods: Descriptive retrospective study of demographic and clinical characteristics of deaths among TB cases notified in Romania in 2007-2009. Data and information have been extracted from electronic National TB Register.

Results: A total of 4920 TB deaths have been reported in the analyzed 3 years: 1657 men in 2008 and 1535 in 2009. Of them 80.8% were men and 58.9% were living in rural area. The highest frequency of deaths occurred in 50-54 years in each analyzed year. The ratio of pulmonary site was 93.4%, with bacteriological confirmation rate by microscopy 71.6% and by culture 63.5%. The share of deaths caused by TB decreased from 62.2% in 2007 to 80.8% in 2008 and 75.4% in 2009. MDR-TB cases represented 8.5%. The most common associated diseases were alcoholism, liver diseases, diabetes and renal diseases. HIV co-infection has been registered in 2.1%.

Conclusions: In the analyzed period of time the highest number of deaths has been recorded in 2008. The highest proportions of TB deceases were observed in men. The age group, living in rural area, most commonly alcoholics, with advanced pulmonary forms of disease.

P4366
Results of retrospective study of TB contact investigations in Iasi County, Romania
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The aim of this study is to evaluate the patients diagnosed as tuberculosis and registered to a Tuberculosis dispensary in year 2010 according to the health care units which they applied beforehand and the time period since first symptom of tuberculosis has occurred. For this descriptive study, the questionnaires which consist of questions about enrolled tuberculosis patients’ characteristics, symptoms, duration between the first symptom and diagnosis and health care units they applied before coming to tuberculosis dispensary have been filled with face to face interviews. Total 127 questionnaires were completed, the majority of patients were male (51.2%). Mean age was 51±20 years. The rate of latent tuberculosis was 59.1% and persons of them had signs of active pulmonary tuberculosis. Among a pathology of organ of the thorax which has been not bound to a tuberculosis acute pneumonia, chronic obstructive pulmonary diseases COPD, and heart disease were the most common symptoms. At diagnosis, 16.4% had diabetes, 10% had chronic bronchitis, and 5.1% had former cancer. Acute pneumonias were 71%, COPD – 16.7%, lung cancer – 4.3%.

P4369
The pathology of a thorax at the men getting to the penal institutions
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The goal of current research was to study a pathology of a thorax at the men getting to the penal institutions. The study has been carrying out during four years in one investigatory isolation ward in Moscow. Fluorographic examinations of all prisoners – 10–17% had chest X-ray. 51.7% received INH preventive therapy 3-12 months. 16.4% had no records about chest X-ray or preventive therapy. At the initial checking of the contacts, 7 active TB cases were detected; other 36 active TB cases were registered in the next 10 years. 62.7% (27) TB cases in contacts were registered in the first year of activity. 5.1% in the next 2 years. 7 contacts with no initial records developed active TB later. Conclusions: 5.1% of the TB contacts developed active TB in the 10 years follow up period of time. Effective contact investigation and prevention of TB spreading in house hold contacts should consider:
- Lack of algorithm for contact tracing (no clear moments for contact follow up after the first control) in the NCC.
- The recommended tools for investigation of contacts were not entirely used, different approaches for preventive therapy regarding number of months, doses, monitoring of treatment, lack of knowledge in the group of patients, their families and GPs’ network regarding the importance of preventive therapy and also about periodic control.

P4367
Tuberculosis in prison
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Introduction: Prison tuberculosis is a major problem because society “behind the walls” is overcrowded and isolation of patients is difficult and time-consuming. The program for improvement of the control on tuberculosis in Bulgarian prisons was started in order to solve these conditions.

Aims and objectives: Our aim is to present the ability of the program to provide better care for patients and contact people and better working conditions for medical personnel on both sides of the walls.

Methods: We observed a one year period from the beginning of the program in the Pleven prison. Measures like regular screening questionnaires, bacteriology, chemical preparations and consultations with a supervising pulmonologist were provided regularly. Patients with pulmonary tuberculosis were isolated and sent to the prison hospital. Contact people were tested with a tuberculin test and were given isoniazid.

Results: This prison is inhabited by 600 prisoners and only 2 of them were diagnosed as sufferers of active tuberculosis. Other 2 continued therapy in prison after active hospital treatment. Prevalence of prison tuberculosis is about 900 out of every 100 000 prisoners. 421 questionnaires were filled. 110 prisoners gave sputum for bacteriology and 52 tuberculin tests were done. A room was built for induction of sputum and another for patient isolation.

Conclusion: The above measures guarantee the ability of the program to provide good medical service to prisoners, however most of them had contracted tuberculosis outside the walls before imprisonment.

P4368
How did the tuberculosis patients reach to a tuberculosis dispensary and how long did it take?
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A strategy targeted to improve the role and efficacy of primary care units in referral of the patients with highly suggestive symptoms to the tuberculosis dispensaries should have the priority to avoid the time lag in diagnosis.

P4370
Forecasting the risk of medicinal complications from the chemical therapy in patients with multi-resistant pulmonary tuberculosis
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Objective: Development of forecasting method for medicinal complications (MC) in patients with multi-resistant pulmonary tuberculosis (MPT). Research methods and materials: 116 patients with MPT which were divided into two groups were examined: the 1st group – 88 patients with MC from chemical preparations and the 2nd group – 78 patients without MC.

Results: For each risk factor was determined risk rate (RR). Important in forecasting were such factors as intolerance to chemical preparations in the past and existence of pernicious habits (RR -1.4), length of sickness from 4 to 5 years (RR-2.25), existence of concomitant diseases (RR – 2.5), existence of fibro-cavernous pulmonary tuberculosis (RR – 1.7), biochemical changes in the liver (RR -2.9) and kidney (RR -3.7), changes in electrolyte metabolism (RR -2.23), leukocytosis (RR – 3.6), existence of lymphopenia (RR – 2.3), increase in ESR (erythrocyte sedimentation rate) to more than 40 mm/h (RR – 2.5), in the age of 30 - 40 years (RR – 1.7). According to decimal logarithm of their production maximal and minimal risk range of MC comprising the value from ~9.9 up to +6.4 were determined.

Conclusion: The developed forecasting method of MC in patients with MPT allows from the first days of sickness forecast the risk level of MC from the chemical preparations.
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resistance related mutations in the rpoB gene were detected in 13/15 (86.7%).

Based on the phenotypic drug susceptibility testing results, 15 (12.1%) was BACTEC culture positive for mycobacteria. Out of 123/165 (74.5%) were M. tuberculosis isolates from EPTB cases and to reveal the main mutations of gyrA gene associated with FQ resistance. DNA samples of M. tuberculosis were collected from 70 adult patients of both genders. Seventy-eight speciments from patients of EPTB cases in tertiary care hospitals in northern India has over 1.982 million incident TB cases per year and world’s 3rd highest HIV burden. The estimated PLWHA is 0.34% (2.38 million) of Indian population. TB-HIV coordination activities are being implemented since 2001.

Methods: The primary defaulters (PD) were identified by comparing the list of patients registered for treatment with the list of patients who did not report for treatment initiation. They were also asked about reasons for not reporting.

Methods: A total of 789 specimens from patients of EPTB cases with varied pre-treatment sample pattern were collected from 70 adult patients of both genders. Seventy-eight specimens from patients of EPTB cases in tertiary care hospitals in northern India has over 1.982 million incident TB cases per year and world’s 3rd highest HIV burden. The estimated PLWHA is 0.34% (2.38 million) of Indian population. TB-HIV coordination activities are being implemented since 2001.

Methods: To identify factors responsible for Cat-I and II relapse among successfully treated tuberculosis (TB) patients under DOTS programme.

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Methods: This paper attempts to assess the drug resistance pattern in the rpoB gene of M. tuberculosis among the patients of EPTB cases in tertiary care hospitals in northern India has over 1.982 million incident TB cases per year and world’s 3rd highest HIV burden. The estimated PLWHA is 0.34% (2.38 million) of Indian population. TB-HIV coordination activities are being implemented since 2001.

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from DOTs clinics. 54.2% of the respondents answered that many of their patients came back and expressed satisfaction. 59.3% of the respondents answered that few of their patients complained of DOTS treatment. The most common negative comment was delayed supply of medications. The most common positive comment was medications are for free. 81.2% respondents did not receive PHILHEALTH incentives for every patient they referred to DOTs. This study recommends to conduct retraining or seminars on private practitioners.

Methods: Initially, we reviewed all kinds of pulmonary mycobacteria isolation from January 2004 to December 2009, based upon the laboratory database with clinical chart. When multiple isolates were detected, species identification was performed for one species per patient per year. Next, we investigated, on the 2009 patients, the initial year of MAC diagnosis during the past 20 years. Thirdly, we followed the course of 2004 MAC patients up to 2009, speculating the yearly accumulation of the disease.

Results: From laboratory data, the yearly number of NTM isolation increased from 353 in 2004 to 488 in 2009 (mean annual increase,5.9%) and from MAC of 291 to 418 (increase 6.8%). Proportion of MAC to all NTM showed a constant value of 81.4%, indicating that increase was due to an increase of MAC. From clinical data, many of MAC patients in 2009 had an initial diagnosis of MAC during the period from 1978 to 2008. Follow up analysis on the cases found in 2004 and having yearly bacteriological examination, showed over half of the positive MAC patients in 2004, were still culture positive in 2009. MAC-related death was observed on 8 cases among the total 99 cases in 2004.

Conclusion: An accumulation of MAC patients in recent years was likely to occur in Tokyo, Japan.

435. Novel strategies for the diagnosis of tuberculosis

P4380 Late-breaking abstract: Expression of IFN-γ/G/L-10 in active pulmonary tuberculosis patients and household contacts
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There is an increase in the prevalence of tuberculosis in young adults. T cell, cytokine mediated immune responses to Mycobacterium tuberculosis infection are important determinants of disease development and pathology, the aim was to investigate the role of candidate cytokines in active pulmonary tubercu- losis patients (APTB) of younger age (15-30yrs) & their HouseHold Contacts (HHC). T cell assays were stimulated with r32-kDa antigen of M. bovis BCG (Ag85A-BCG). IFN-γ & IL-10 were measured in the culture supernatants by ELISA in APTB (15); HHC (PPD-positive) (15) & Healthy Controls (HC) (PPD status not known) (15). Expression levels were determined by quantitative real-time PCR in 4 individuals from each group. The mean proliferative responses of stimulated cells were significantly low (p<0.05) in APTB and HHC compared to HC (1.53±0.72; 1.55±0.89 and 4.4±4.43) respectively. The mean IFN-γ (p<0.05) (43.4±24.8; 46.0±22.2 & 70.9±4.41) & IL-10 (85.7±5.87; 63.0±4.42 & 11.4±7.7 gp/l (p<0.003 & <0.0006) levels were significantly low and high respectively in APTB & HHC when compared to HC. The expression of IFN-γ was high (5-fold) in HC when compared to APTB (1.5-fold) & HHC (3-fold), against the corresponding unstimulated cells. IL-10 expression increased by 8- fold in APTB & 6-fold in HHC compared to HC (2-fold). In conclusion, elucidation of the mechanism by which Th1 cytokine is down-regulated may enhance our understanding of susceptibility to disease. Also, follow-up of the contacts for their clinical status may help in identifying a biomarker for house-hold contacts useful for early diagnosis.

P4381 Analysis of C-reactive protein and fibrinogen as possible predictors of secondary fibrosis in pulmonary tuberculosis
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Aim: To study the influence of C-reactive protein (CRP) level in the blood, fibrinogen level and general inflammatory syndrome as the predictors of development of secondary fibrosis in patients with pulmonary tuberculosis (TB).

Methods: Concentration of CRP, fibrinogen level was measured using immunomunobidimetric method including criteria was presentation of TB process in both lungs, as the sign of widespread TB process.

Results: We examined 85 patients treated in one year. Mean CRP level was 22.6 mg/mL, range 5-245 mg/mL; normal level (up to 8 mg/mL) was measured in 23.4% patients, medium level (9-20 mg/mL) was measured in 31.3% patients, high level (21-50 mg/mL) were measured in 26.2% patients, and in 23.7% patients CRP were higher than 50 mg/mL. Average fibrinogen level in whole group was 6.9 g/L (SD 5.8). Normal level of fibrinogen (up to 4 g/L) were measured in 6.4% of patients; 4.1-10 g/L were measured in 24.6% patients, 10.1-20 g/L were measured in 31.1% patients and level more than 20 g/L were measured in 37.9% patients. Using statistic method of partial correlation statistical significance at level p<0.05

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was shown between them. Correlation of CRP and fibrinogen level with appearance of fibrinosis on X-ray of the lung was shown. Thereafter, closer correlation was shown between fibrinogen and fibrinosis than with CRP and fibrinosis.

Conclusion: Predicted value of CRP and fibrinogen for pulmonary fibrosis was shown in TB patients. So, attenuation of fibrinosis development, possible with antifibrotic activity of pentoxiphyllin, should be taken in consideration, for prevention of widespread development of lung fibrinosis in these patients.

**P4382**

Decreasing level of serum ADA: A valuable predictor of treatment in smear positive tuberculous pleuritis

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Background: High titer of adenosine deaminase (ADA) in pleural fluid is an indicator of pleural tuberculosis and necessity of treatment initiation. On the other hand high serum ADA of ADA is a characteristic of tuberculosis, and is used for treatment follow up in patient on standard antituberculosis regimen. Decreasing level of ADA could be a predictor of treatment response.

Methods: A cross sectional study was carried out on 29 patients from Sep 2007 till Dec 2010. All of the tuberculosis patients included had a positive sputum smear or positive biopsy or bronchoalveolar lavage (BAL). ESR and ADA were checked for these patients in treatment initiation, 30th and 60th day of treatment. According to ADA diagnostic kit values, ADA more than 15 is high.

Results: Mean age of the patients was 38.9 ± 6.2 years. Mean ADA before therapy was 19.31 which gradually decreased to 12.37 (on day 30) and 11 (day 60). Mean ESR before initiation of therapy was 65 which decreased gradually to 38.66 (day 30th) and finally 23.28. Male patients were 55.2%, 82.8% suffered from pulmonary TB. Comparison of ADA and ESR at the end of therapy showed a significant difference (p=0.000). Mean ADA (60th day) in males was 11.18±1.60 and in females were 10.76±0.42. Mean ESR (60th day) in males was 25.50±5.48 and in females was 23.03±2.02.

Conclusion: Decreasing level of serum ADA is a valuable and reliable predictor in successful treatment of tuberculosis.

**P4383**

Adenosine deaminase, an useful tool for the diagnosis of tuberculous pleuritis in France

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Pleuritis is a diagnosis challenge for usual mycobacteriological analysis given that the bacillary concentration is low in the pleural effusion. Adenosine deaminase is a pleural inflammatory marker recommended for the diagnosis of pleural tuberculosis in the high-prevalence countries. There is not enough data to support its use in a low-prevalence country.

Objective: To know the utility of ADA for the diagnosis of pleural tuberculosis in France, a low prevalence country.

Material and method: Retrospective study of the exudative pleural effusion with the ADA dosage (Giusti’s method) done in two military hospital near Paris. We compared tuberculous and non-tuberculous pleural effusion. The best cut-off value of ADA for the diagnosis of pleural tuberculosis was found using ROC curves.

Results: 183 patients were studied, including 29 tuberculosis, 65 cancers, 5 malignant hemopathies, 32 parapneumonic pleural effusions, 24 purulent pleuritis, 12 old transudative effusions, 14 effusions from other aetiologies. Sixty-eight effusions were rich of lymphocytes including 23 tuberculosis. The young age (<35 years-old), the foreign origin and the presence of general manifestations were independently associated with tuberculosis. The best cut-off value for ADA was 47 U/L with Se: 95.7%, Spe: 91.6%, PPV: 84.6%, NPV: 97.6%. When ADA ≥ 70 U/L, the PPV was 90.5%.

Discussion: ADA dosage is useful in France. Lower than 47 U/L, it may exclude tuberculosis. When ADA ≥ 47 U/L, the result should be interpreted considering the context and the pre-test probability of tuberculosis. When this pre-test probability of tuberculosis is important, ADA ≥ 70 U/L is very likely for tuberculosis.

**P4384**

Clinical utility of a lateral flow serologic test in the rapid diagnosis of pulmonary TB in a public-private mix for DOTS setting in Iloilo City, Philippines

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Background & rationale: Diagnosis of PTB in a developing country with a limited resource relies largely on clinical features, sputum exam and chest xray. In an endemic area such as the Philippines, the urgent implementation of intensified case-finding and infection control measures which reduce the burden of TB is essential to saving lives. Culture methods are not routinely used in the locality due to the low cost-effectiveness and time constraints. By using serological methods, the time required to reach a clinical decision to treat a suspected case of TB may be significantly reduced. We have investigated the utility and diagnostic accuracy of a lateral flow serologic test in PTB diagnosis when used as an adjunct in the Fire-DOTS setting.

Methods: An immuno-chromatographic TB STAT PAK II Assay was employed for the detection of antibodies to M. tuberculosis in the human whole blood of TB suspects. Humoral response was analyzed in a group of 105 TB suspects (74 in the active PTB group - 47 smear-positive and 31 smear-negative, and 31 in the non-active/control group - 31 smear-negative and 6 healthy subjects).

Results: The proportion of all test subjects with PTB who tested positive was the assay was 65%, while the proportion of all subjects without PTB who tested negative was 100%. The positive predictive value (PPV) and the negative predictive value (NPV) was 100% and 50.94%, respectively.

Conclusion: The serologic test performed with excellent specificity and acceptable sensitivity in PTB diagnosis in an endemic setting, though not enough evidence exists that they perform well enough to replace sputum microscopy.
Background: The suboptimal sensitivity of IFN-γ-based assays, especially in immunocompromised individuals, emphasizes the need for alternative markers for diagnosing tuberculosis (TB). Objective of this study was to evaluate whether IFP-10 can be a useful biomarker for evaluating a specific response to RD1 antigens associated to active TB in HIV-infected individuals. Control with QuantiFERON-TB Gold In tube (QFT-IT) was performed.

Methodology: 118 HIV-infected individuals were prospectively enrolled in Rome, 21 with active TB and 98 without. Epidemiological characteristics and laboratory data were recorded. IFN-γ and IFP-10 response to QFT-IT was performed. Plasma was harvested at day-1 and soluble factors evaluated by ELISA.

Results: Significant differences between those with or without active TB were found for the CD4+ T cell counts (p=0.02), and IFN-γ and IFP-10 response to QFT-IT (p<0.001 for both analysis). Diifferently no significant differences were found for the age and HIV-RNA. Based on the commercial cut-off of the QFT-IT and on a cut-off found by ROC analysis for the IFP-10-based responses, the sensitivity for active TB of QFT-IT and the IFP-10 to QFT-IT was 52% and 67% respectively (p=0.001; K: 0.545). The response to IFP-10 was not influenced by the ability to respond to the mitogen. The specificity for active TB of QFT-IT and of the experimental test were 84% and 77% respectively (p=0.01; k: 0.710). Among those without active TB a significant correlation between a positive score and MIP expression was found (p<0.001).

Conclusions: These data suggest that IFP-10 is an additional marker to evaluate the RD1-specific responses in HIV-infected subjects confirming data previously obtained in high TB endemic countries.

Objective: To assess whether urinary levels of neopterin can discriminate between latent and active mycobacterium tuberculosis infection.

Methods: Urinary neopterin/creatinine ratio’s were determined in patients with active and latent m. tuberculosis infection and controls without m. tuberculosis infection. Latent m. tuberculosis infection was defined as reactive interferon gamma release assay for m. tuberculosis in the absence of active disease.

Results: Seven patients with active tuberculosis, 27 patients with latent m. tuberculosis infection and seven controls were recruited. There was no difference in age or gender between groups. Urinary neopterin/creatinine ratio was higher in patients with active tuberculosis (412.8 micromol/mol, 95% CI 89.7 to 735.8) than patients with latent m tuberculosis infection (147.5 micromol/mol, 95% CI 114.0 to 180.8) and controls (122.2 micromol/mol, 95% CI 71.2 to 173.1) (p<0.01). ROC curve analysis revealed an area under the curve of 0.81 (95% CI 0.62 to 0.99). A cut-off of 349 micromol/mol showed 100% diagnostic specificity in detection of active tuberculosis in people with m. tuberculosis infection.

Conclusions: Urinary neopterin/creatinine ratios are significantly higher in patients with active tuberculosis compared to patients with latent m. tuberculosis infection. These findings suggest that neopterin appears to be a suitable marker to reflect tuberculosis disease activity.

Introduction: Early referral of patients with suspected tuberculosis (TB) has a significant impact to clinical outcomes (leading to shorter infectivity and reduced morbidity and mortality rates).

Aim: To identify factors contributing to delays in the diagnosis of intra-thoracic (pulmonary, mediastinal and pleural) TB.

Methods: A retrospective case review of all patients who were diagnosed with intra-thoracic TB (January 2003 to January 2011) in Queen Elizabeth Hospital, Woolwich. Allowing for a chest X-ray (CXR) turnaround time of 3 weeks and a median period of 7 days between TB diagnosis and commencing treatment, we reviewed the full radiological history of all patients for whom the cut-off period of 28 days was exceeded. Delayed cases were divided into five groups, according to the reason for the delay:

1. Clinical diagnostic delay (unreported/misreported CXRs)
2. Delayed referral to specialist services
3. Pleural effusion (CXR’s with effusions, subsequently proven to be tuberculous)
4. CXR’s with concurrent pathologies
5. Lost to follow up

Results: 634 intra-thoracic TB notifications were made within the specified time period. 121 patients (19%) had at least one abnormal CXR taken 28 or more days prior to starting treatment (group 1: 38, group 2: 43, group 3: 16, group 4: 8, group 5: 16). The time delay between first abnormal CXR and starting treatment varied considerably (median: 69.5 days, range: 29–1020 days) and was greater in male (73%) and Asian patients (40%). 32 patients (26.4%) were sputum smear positive.

Conclusion: The diagnosis of RTB is delayed for a significant number of patients and appropriate measures should be taken in order to minimise such delays.

Introduction: Patients with suspected pulmonary tuberculosis and negative sputum samples constitute a problem that is not uncommon in clinical practice. Fiberoptic bronchoscopy is an alternative method of collecting respiratory samples that plays an important role in such cases.

Objectives: The aim of this study was to assess the yield of bronchoalveolar lavage in early diagnosis of negative sputum smear pulmonary tuberculosis and its impact on management.

Methods: The study was conducted for 27 months in a central hospital. Bronchoscopy was performed in patients after three consecutive negative sputum smears for acid-fast bacilli, in United Kingdom.

Results: In the overall diagnostic yield of fiberoptic bronchoscopy was 39% (39 out of 100) and included 18% of other diagnosis than tuberculosis with 3 cases of malignant disease. Through bronchoalveolar lavage smear and nucleic acid amplification test for M. tuberculosis an immediate diagnosis was obtained in 57.1%. Median time to positive culture was lower in bronchoalveolar lavage compared to supposed smear (p<0.001). The global resistance to antituberculosis drugs was 19%.

Conclusions: Bronchoalveolar lavage samples were helpful in the management of
smear negative pulmonary tuberculosis. The procedure had good diagnostic yield and contributed to the diagnosis of other diseases.

**P4391**
Diagnostic accuracy of sputum induction test compared with bronchoscopic results to confirm of diagnosis of pulmonary tuberculosis

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**Rationale:**
Diagnosis of pulmonary tuberculosis is difficult in patient who do not produce sputum spontaneously, or who have AFB smear (-) sputum. Bronchoscopy is helpful in these patients, but in many cases cannot be readily available. We prospectively compared the diagnostic yield of sputum induction test with bronchoscopy.

**Methods:**
Between February 1 to July 31, 2010, we included the patients suspected active pulmonary tuberculosis, who could not produce sputum spontaneously, or who had a pair of AFB smear (-) sputum. They underwent sputum induction test and bronchoscopy. We calculated the sensitivity of AFB smear, culture for Mycobacterium tuberculosis, TB-PCR of each test, and evaluated the concordance rate by kappa test.

**Results:**
Sensitivities of AFB smear were 36.1% in sputum induction test and 33.3% in bronchoscopy. Sensitivities of culture for Mycobacterium tuberculosis were 69.4% and 75.0%, and TB PCR were 52.8% and 58.3% in sputum induction and bronchoscopy, respectively. The results of AFB smear by sputum induction and bronchoscopy were concordant in 94% (63/67 case, Kappa test=0.819). In culture for Mycobacterium tuberculosis, the results were concordant in 82% (54/67 case, Kappa test=0.684) and the results of TB-PCR were concordant in 88% (59/67 case, Kappa test=0.75).

**Conclusions:** In this study, sputum induction test had shown similar diagnostic value and sensitivity with bronchoscopy in the diagnosis of active pulmonary tuberculosis. In patients who are difficult in collecting sputum, or have AFB smear-negative sputum, sputum induction test can be an alternative approach to the diagnosis of active pulmonary tuberculosis.

**P4392**
Use of fiberoptic bronchoscopy in early diagnosis of sputum smear-negative pulmonary tuberculosis

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**Background:** Pulmonary tuberculosis (PTB) is a major health problem worldwide. Rapid diagnosis allows early treatment and infection control, which is hard to achieve among sputum smear-negative (SSN) subjects. Different bronchoscopic sampling techniques have been used but their roles remain unclear.

**Objectives:** To evaluate the value of fiberoptic bronchoscopy in the diagnosis of PTB among SSN patients in a regional hospital in Hong Kong.

**Methods:** Medical records of 22 patients, who have undergone bronchoscopy in the North District Hospital, HK SAR, in 2009, and were later diagnosed of having PTB, were reviewed. Results of their pulmonary specimens were recorded. The exclusive diagnostic test was identified.

**Results:** Bronchoalveolar lavage (BAL) was performed in all 22 cases. Positive acid-fast smear and culture were obtained in three (13.6%) and six cases (27.3%) respectively, providing the exclusive means of diagnosis for four cases (three from smear, one from culture). Molecular study from BAL was done in 14 cases, in which five cases were test positive (35.7%), two cases gave exclusive diagnosis. Transbronchial lung biopsy (TBLB) was performed in 19 cases. All were sent for histology, while six were sent for acid-fast bacilli (AFB) culture. Histology gave positive results in five cases (26.3%), which was the exclusive means of diagnosis for two. TBLB AFB smear was all negative, but three gave positive AFB culture. Among them, one provided exclusive diagnosis.

**Conclusion:** While sputum examination remains the cornerstone in diagnosing PTB, fiberoptic bronchoscopy plus various sampling techniques served as a useful adjunct to optimize the diagnostic yield, especially among those SSN cases.

**P4393**
Rapid molecular detection of rifampicin and isoniazid resistance and identification of mutations in resistant genes of multi-drug resistant tuberculosis (MDR-TB) patients

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Recently identification of mutations responsible for drug resistance by molecular methods are used to detect antimycobacterial resistance in MDR-TB patients and to overcome difficulties of treatment planning in some TB patients. In our study 29 patients were evaluated - 16 patients who were treated with minor therapy or with suspicion of MDR-TB and 13 patients with treatment failure, relapsing and returning after defaulting, who were taking retreatment regime. Mutations in rpoB, katG and inhA gene zones specific for rifampicin and isoniazid were investigated with molecular methods in 14 patients from direct smear positive samples and in 15 patients from positive culture. AFB stain, culture and drug susceptibility testing with BACTEC 460 were also done for all samples. 28 samples (22 MDR-TB, 5 susceptible to four drugs, 1 culture negative) were identified as M. tuberculosis complex, 1 patient was detected as M. intracellulare. 27 Patients were who culture positive for MTFB were positive with molecular methods, 1 patient who was determined as MDR-TB and isoniazid resistance was detected in 21 (9/5.5) patients. In 5 patients who were susceptible to four drugs, no mutation was found. In 3 patients with HR resistance, cure was achieved with retreatment regime.

**Conclusion:** The detection of HR resistance with molecular methods is a guide to diagnosis of MDR-TB patients andshortens the time to starting of MDR-TB treatment.

**P4394**
Real time polymerase chain reaction (RT-PCR) based rapid detection of multi-drug resistant (MDR) mycobacterium tuberculosis (MTB)

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**Objective:** Rapid confirmation of diagnosis of MTB and MDR-MTB in clinical samples by RT PCR and Melting Curve Analysis (MCA).

**Introduction:** TB is one of the leading causes of mortality in world. An extremely worrying aspect of MTB is the recent rise in MDR- MTB cases in several countries. The culture based diagnostic procedures takes weeks to detect TB and its drug resistant variants. In developing countries this delay could compromise efforts to interrupt TB transmission. There is, therefore, intense interest to develop rapid and precise molecular diagnostic methods.

**Methods:** DNA was extracted from sputum or body fluids of about 100 patients suspected of TB. MTB diagnosis was confirmed by RT PCR amplification and subsequent melting curve analysis, with MDR confirmation by MCA.

**Results:** In culture positive results in five cases (26.3%), which was the exclusive means of diagnosis for four cases (three from smear, one from culture). Molecular study from BAL was done in 14 cases, in which five cases were test positive (35.7%), two cases gave exclusive diagnosis. Transbronchial lung biopsy (TBLB) was performed in 19 cases. All were sent for histology, while six were sent for acid-fast bacilli (AFB) culture. Histology gave positive results in five cases (26.3%), which was the exclusive means of diagnosis for two. TBLB AFB smear was all negative, but three gave positive AFB culture. Among them, one provided exclusive diagnosis.

**Conclusion:** While sputum examination remains the cornerstone in diagnosing PTB, fiberoptic bronchoscopy plus various sampling techniques served as a useful adjunct to optimize the diagnostic yield, especially among those SSN cases.
436. Treatment of pulmonary mycobacteriosis and adverse drug reactions

4398 Efficacy and safety of linezolid for the treatment of multidrug-resistant tuberculosis (MDR-TB) and disease by non tuberculous mycobacteria (NTM)

Linezolid's (L) long-term use in the treatment of MDR-TB and NTM may be limited by its serious adverse reactions. Aim of this study was to evaluate the efficacy and tolerability of a daily dose of 600 mg of L in combination with other drugs against mycobacteria, in patients with culture proven MDR-TB and NTM disease.

Method: Between Sept 2008 and Jan 2011 in our TB Unit/Outpatient Clinic we followed 34 MDR-TB + XDR-TB and 18 NTM pts. Of them, 19 pts (2 XDR, 4 NTM), all HIV (+), had been treated with L which was added to regimens for 4-24 months (median 17). Spu腾 cultures, blood count/chemistry, ophthalmologic and neurologic examination were undertaken on a regular basis.

Results: 16 pts completed treatment and were cured. Culture became negative in all pts in an average of 14-32 weeks. One died after 5 months of treatment due to chronic respiratory failure and progressive M. avium disease, 2 discontinued (no adherence) after 5 and 7 months. 3 of 16 pts experienced adverse events, which led to withdrawal of L in all 3 pts developed bone marrow depression and one optic neuropathy. Blood transfusions were given to both pts and bone marrow function normalized after cessation of L.

Conclusion: Linezolid seems highly effective in combination treatment of MDR-TB, XDR-TB and NTM disease. The majority of patients on L had positive treatment outcomes. All pts under L treatment should be monitored closely for presence of serious adverse reactions.
regimen, tailored by drug susceptibility tests, as 4th, 5th or 6th drug for 4-20 weeks. XDR was the strict indication for Lz, MDR - only if found impossible to create the adequate chemotherapy regimen (min 4 drugs) due to intolerance and/or resistance to second-line drugs.

**Results:** After 4 weeks of treatment in all cases the evident resolution of clinical and X-ray symptoms was obtained. The sputum smear negative was achieved totally score 85.5% (30 pts) 73.3% after 8 weeks, additional 6.7% after 12 weeks and 3.3% else after 16 week. The severe side-effects, attributed to Lz, occurred in 2 pts (5.7%): pereoneal neuropathy and obstinate vomiting. Anemia, thrombocytopenia were not registered.

**Conclusion:** The regimens included L (min 8 week) are high-effective in MDR and XDR BT in spite of long-term ineffective previously treatment. The Lz safety is quit well over a period of 8-16 weeks. Lz must be considered as a drug of choice after obtaining more accurate information on optimal length of administration, taking into account its high price.

**P4403**

**Linezolid in complex treatment of XDR-TB patients**

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**Department:** TB Department, Central TB Research Institute, Moscow, Russian Federation

**Objectives:** To assess efficacy of treatment of XDR TB patients with linezolide.

**Materials and methods:** Treatment of 78 XDR TB patients, enrolled in this study, consisted besides chemotherapy of collapse therapy, additional albunimous nutrition, and also supporting therapy, aimed at prevention of possible side effects. All TB patients were treated with Cm, Mtx, Cs, PAS, Prn, Z, Amoxic and Cil. Patients were divided into two groups: main group included 44 patients who received complex treatment and linezolide in the dose of 600 mg per day during 6 months and the other group (controls) consisted of 34 patients receiving the same complex treatment without linezolide. Therapy results were assessed in 12 months by frequency of negatiation of M. tuberculosis with a culture method and by clinical and X-ray dynamics of a treatment process.

**Results:** Culture method confirmed that 77.3% of patients became cultures negative in 12 months in the main group and only 35.3% of patients in the group of controls (p<0.05). In the main group in 12 months 18 (40.9%) patients showed healing of cavities and resolution of infiltrations, 16 (36.4%) patients had closing of cavities from one side with expressed resolution of infiltration, 8 (18.2%) patients had positive clinical and X-ray dynamics with reduction of the size of a destruction. In the group of controls there were observed healing of cavities and resolution of infiltrations at 8 (23.5%) patients; positive X-ray dynamics and healing of destructions from one side at 2 (5.9%) patients, p<0.05.

**Conclusion:** Inclusion of linezolide into regimen of chemotherapy for XDR TB patients significantly increases efficiency of their treatment.

**P4402**

**Adverse events in the treatment of multidrug-resistant tuberculosis**

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**Objective:** To study the frequency and nature of side effect in patients receiving second line anti TB drugs.

**Introduction:** Ojha Institute of Chest Diseases (DHUS) Karachi Pakistan is managing drug resistant TB patients since 1996. Adverse events associated with second line drugs have a severe impact on adherence. Frequency of adverse events is not studied in resource-limited settings. Since 2009 patients are being managed according to WHO guideline. Treatment regimen is tailored i and data management j and account of side effect is maintained

**Method:** Patients registered from 1st 01 – 2009 to 30-09-10 were included Data from DR TB 60 was recorded in Microsoft excel and o SPSS 16 and analyzed.

**Results:** 440 patients were registered.Age range from 9 -76 year (mean 32.9)., ratio of male to female was 54:7: 45:3. 99.3% had pulmonary tuberculosis Abdominal symptom were present in 51.4%, heart burn 48 (11.3%), abdominal pain/discomfort in 71 16.7%, epigastric pain in 29.3, nausea and vomiting in 28.2.

Vertigo observed in 140 (31.7%), hearing loss in 3.5% Depression in 5%, anxiety in 22 (5%), headache in 56 (12.7%) and 0.7% had uraemia.Psychosis in 12 (2.8%) y one had seizure, 4 joint pain. Hypothyroidism in 15 patients. Mild itching present in 7.5% cases one had exfoliated dermatitis. The onset of symptom was from seven days to 120 day. Most patients responded to symptomatic treatment. Drug were transiently stopped in patients with psychosis, completely in patient with exfoliative dermatitis and changed in 02 patients with gasteritis and one with psychosis.

**Conclusion:** Gastrointestinal event were most frequent. Treatment can be continued with treatment of adverse event in most of the cases.

**P4404**

**Adverse events during treatment for latent tuberculosis infection**

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**Method:** Records of all patients who received treatment for LTBI at the Chest Clinic of a large tertiary hospital between 01/2000 and 04/2008 were reviewed. An adverse event was defined as any change in health status that led to treatment interruption or cessation. Liver function tests were not performed routinely during follow-up, except when the patient was considered to be at an increased risk of developing hepatitis.

**Results:** Of 201 patients in whom treatment for LTBI was initiated 143 (71%) received isoniazid for 6 months, 32 (15%) received a combination of isoniazid and rifampicin for 6 months, and the remainder were treated with different regimens. Their mean (SD) age was 21 (17) years and 44% were male. Nineteen patients (9.5%) experienced an adverse event. Seven patients developed a rash, four had encephalopathy and/or mood disorder, three had subclinical hepatitis, four experienced severe nausea, vomiting and/or other gastrointestinal symptoms and three had features of peripheral neuropathy. In eight patients who experienced an adverse event medication was temporarily ceased and then re-started without change; in four the treatment was ceased, and in seven the treatment was ceased completely. The risk of adverse events was not significantly related to age, sex, drug regimen (single drug versus combination therapy) or baseline transaminase levels.

**Conclusion:** In this cohort almost 1 in 10 patients on treatment for LTBI experienced an adverse event. Although the adverse events were generally mild to moderate, this risk has to be taken into account when deciding whether to advise treatment for LTBI.

**P4405**

**Severe adverse effects of antitubercular drugs and patient management**


**Pulmonary Department, Charles Nicolle Hospital, Tunis, Tunisia**

**Introduction:** Tuberculosis is an infectious disease which can be totally cured by combining antitubercular drugs. Current therapeutic regimens with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin have proved successful in treating tuberculosis. However, they are associated to a high rate of adverse effects that can lead to therapeutic failure.

**Patients and methods:** We retrospectively reviewed records of patients who present severe adverse effects of antitubercular drugs. We also examined the frequency of and reasons for changing drug regimens.

**Results:** Thirty two patients (20 men) mean age 47 years (18-80 years) were enrolled. Predominant locations of tuberculosis were pulmonary (40%). Cutaneous manifestations were the most frequent (40%) of cases, predominantly
uricartrial associated with fever in 6 cases. Anemia was noted in two cases and thymomascopy was noted in one case, anaphylactic shock in two cases, a systemic toxicemia in two cases and renal failure in one patient. Interrupting either one drug or the whole treatment was necessary to define the cause of the reaction. The clinical evolution of hypersensitivity signs was favorable in all cases following definitive withdrawal of the responsible drug. Complete recovery from tuberculosis occurred in all cases. Rifampicin was inerminated in 15 cases, pyrazinamide in 9 cases, isoniazid in 4 cases, streptomycin in 4 cases and Ethambutol in 1 case. Interrupting either one drug or the whole treatment was necessary to define the cause of the reaction. The clinical evolution of hypersensitivity signs was favorable in all cases following definitive withdrawal of the responsible drug. Complete recovery from tuberculosis occurred in all cases.

P4406

Individualized treatment regimens with second line anti-TB drugs (SLD) compared to first line anti-TB drug (FLD) only in new pulmonary TB patients, culture confirmed with full sensitivity at drug sensitivity test (DST)

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Constantin Marica. Tuberculosis, Institute of Pneumology “Marius Nasta”, Bucharest, Romania

Background: SLD are known as less efficient than FLD. However in clinical practice some of new pulmonary confirmed, fully sensible at DST TB cases are treated with individualized anti-TB regimens containing SLD.

Material and methods: In Romania, 3845 new pulmonary culture-confirmed TB cases, with full sensitivity at DST registered between 01.01.2006-31.01.2007 were analyzed for anti-TB treatment regimen, treatment outcome, duration of treatment. Results: Out of 3845 cases, 79 (2.1%) cases were treated with regimens containing at least one SLD for at least one month and 3766 (97.9%) were treated with FLD only. Out of 79 cases treated with mixed FLD-SLD, 61 (77.1%) were successfully treated. Out of 3766 cases treated with FLD only 3309 (87.7%) were successfully treated. The difference between the success rates was statistically significant (p<0.001). The medium duration of treatment among the 79 cases treated with mixed FLD-SLD was 47 weeks (3 weeks more than a standard category I anti-TB regimen had last 24 weeks).

Conclusions: Individualized treatment regimens with SLD should be kept only for very few cases with severe adverse reaction against FLD. NTP’s must assure uninterrupted supply with at least FLD

P4407

Monitoring of antituberculous drugs adverse events during the treatment of multidrug-resistant pulmonary tuberculosis

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Setting: The known determinants of drug-resistance development are non-compliance with prescribed treatment. Clinical management of multidrug-resistant tuberculosis (MDR-TB) requires lengthy multidrug regimens that often cause adverse events. Interruptions in treatment may result from the adverse events.

Design: We retrospectively reviewed medical records of 220 patients with MDR-TB who received individualized treatment in accordance with the recommendations of the WHO. A multiple logistic regression model was performed to determine whether the occurrence of adverse reactions was associated with poor treatment outcome.

Results: One or more adverse events were observed in all patients in the study. With an average of one patient receiving treatment, noted 10.4 episodes of adverse events. The most commonly reported events were nausea and vomiting (61%), dizziness (56%), abdominal pain (39%), arthralgia (31%), ototoxicity (19%) and hepatitis (19%). The most commonly reported events were nausea and vomiting (61%), dizziness (56%), abdominal pain (39%), arthralgia (31%), ototoxicity (19%) and hepatitis (19%). With an average of one patient receiving treatment, noted 10.4 episodes of adverse events. Obtained data allow to predict possible adverse events of MDR-TB chemotherapy, to provide the availability of medications necessary for adverse events reduction, including emergency cases.

P4408

Incidence and timing of hepatotoxicity due to anti-tuberculosis treatment

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Hepatotoxicity is a life threatening complication of anti-tuberculosis treatment. It is unclear how closely to monitor liver enzymes during treatment. In the absence of liver risk factors, the American Thoracic Society advises checking them if symptoms develop. The aim of this study was to assess the timing and causative factors associated with hepatotoxicity.

We reviewed patients treated for TB in Leeds between 2006 and 2010. Elevations of aminotransferase (ALT) greater than two times the upper limit of normal (ULN) were noted in 22% (46 patients) of all cases. Our local policy recommends that patients should have ALT checked at weeks 0, 2, 4 and 8. 634 patients underwent treatment for TB during this period. 46 (7.3%) patients had ALT elevations of 2 times ULN. 14 patients (2.2%) five times ULN. Interestingly, hepatotoxicity was more common in Caucasians (p=0.02) and increasing age (p=0.07). Gender, HIV status, pregnancy, and organs affected by TB did not predict hepatotoxicity. The average time for the hepatotoxicity to develop was 28 days (range 3-306); however, this time was increased to 42 days (4-306) in patients with ALT rises greater than five times ULN. Only one patient presented with clinical symptoms of hepatitis, this patient subsequently died from liver failure. In the 14 patients with rises five times ULN, the cause was felt to be pyrazinamide in 8, isoniazid in 3, rifampicin in 1, and not established in 2. It is unknown whether identifying an elevated ALT and stopping treatment prior to symptoms reduces the severity of liver injury. We feel that careful biochemical monitoring and prompt cessation of treatment is appropriate. Only 2 patients developed hepatitis with ALT five times ULN at a time point beyond our 8 week protocol.

P4409

Antituberculosis fixed multi-dose combination and single drug therapy in hepatitis patients

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Background: Fixed dose combinations (FDCs) in tuberculosis (TB) therapy reduce the number of tablets to be consumed, simplify the medication regimen and potentially improve compliance.

Aim of study: Compare the efficacy and acceptability of anti-TB FDCs as single tablets (ST) in patients with active TB.

Patients and methods: A total of consecutive 49 patients (57 men and 37 women; mean age 38,±3.3 years) were randomly distributed into 2 groups: trial group (n=41) patients treated daily with anti-TB FDCs and control group (n=53) treated with individualized regimens (single tablets).

Results: Stratified analyses showed a similar pattern for all the group demographic, clinical and radiologic finding. The dosage of isoniazid, pyrazinamid and ethambutol was adequate in all patients. For rifampicin, dosage was statistically too low in trial group (p=0.04). Serious adverse events were noted in 39% cases of trial group vs 11.5% cases in control group. According of cutaneous reactions (7.3% vs 5.7%) and toxic hepatitis (7.3% vs 5.7%) there was no statistically difference in 2 groups. Hematologic sequellae was noted in 51% in trial group vs 36% in control group.

Conclusion: The efficacy of the anti-TB FDCs regimen was non inferior to that of the standardized regimens. But, hematologic effects were significantly higher in the group of patients treated with anti-TB FDCs.

P4410

Allergic reactions to rifampicin in tuberculosis treatment

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Introduction: Immuno-allergic reactions to antituberculous treatment occur in 4 to 5% of cases and cause serious problem in the management of tuberculosis especially when due to major drug such as rifampicin. Aim of the study: To describe different allergic reactions to rifampicin, the means of their confirmation and their management. Methods: Retrospective study including all patients treated for tuberculosis (TB) and who developed allergic reactions to rifampicin between January 2000 and December 2009. Results: Twelve (12) patients were included with mean age of 42 years. Mean delay of symptoms was 30 days after antituberculous treatment onset. Cutaneous reactions were noted in 11 patients, fever in 5 patients and anaphylactic reactions in 2 patients. Two patients had hepatitis, 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients. In 2 cases the occurrence of thrombocytopenia with hemoragic syndrome and 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients. In 2 cases the occurrence of thrombocytopenia with hemoragic syndrome and 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients. In 2 cases the occurrence of thrombocytopenia with hemoragic syndrome and 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients. In 2 cases the occurrence of thrombocytopenia with hemoragic syndrome and 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients. In 2 cases the occurrence of thrombocytopenia with hemoragic syndrome and 4 had hepatic cytolysis. Rifampicin responsibility was admitted after interruption of all the treatment and reintroduction one by one in 10 patients.

Conclusion: Severe allergic reactions to rifampicin are rare but can cause serious problem in tuberculosis management. In these cases rapid oral desensitization represent an interesting alternative.
P4411 Incidence of peripheral neuropathy during daily TB chemotherapy: Indian experience
Tushar Sahabuddhe, Vikas Oswal. Department of Pulmonary Medicine, Padmashree Dr. D.Y. Patil Medical College, Pune, Maharashtra, India

It is a routine practice to prescribe prophylactic pyridoxine to patients on TB chemotherapy to prevent Isoniazid induced neuropathy. However this adverse effect seems to be uncommon in our experience. We did a prospective study to determine the incidence of peripheral neuropathy in patients on daily TB chemotherapy. A total of 559 patients on standard daily TB chemotherapy as per WHO categorization were followed throughout the course of treatment. No patient received prophylactic pyridoxine. Patients with proven or suspected drug resistance were excluded from the study. Patients with existing peripheral neuropathy or those suffering from a condition predisposing to neuropathy such as diabetes, were also excluded. Patients reporting with symptoms of peripheral neuropathy such as tingling, numbness and other paraesthesia during the TB chemotherapy were followed. Other causes of neuropathy were ruled out. They were given daily vitamin B-complex (containing Pyridoxine 3 mg) one tablet thrice a day for one week. They were given 100 mg Pyridoxine daily only if there was no response. A total of 265/559 patients (4.65%) developed neuropathy symptoms. 19/26 (73.07%) patients responded to one week course of B-complex and never had recurrence of symptoms. 7/559 (1.25%) patients needed 100 mg of pyridoxine to relieve their symptoms. This indicates very low incidence of peripheral neuropathy in patients on daily TB chemotherapy without use of prophylactic pyridoxine, in Indian scenario.

P4412 Ethambutol induced bullous and lichenoid skin eruptions
Ina Ackerl, 1, 2, 3, 4 Dorina Greb, Haifa Zaibi, Med Lamine Meglich. 1Service Ben Nefiss, Hôpital Abderrahman MAMI, Ariana, Tunisie

Introduction: Ethambutol is an essential drug for tuberculosis treatment. It has been in use since 1961. Its major side effect is on visual system, cutaneous side effects are rarely described in the literature including purpura, pruritic erythematous papules and exfoliative dermatitis.

Materials and methods: We report one case of ethambutol induced bullous and lichenoid skin rashes confirmed by provocation test.

Results: It's about 73 years old woman, diabetic, treated of lung tuberculosis with Isoniazid, Rifampicin, pyrazinamid and ethambutol. After 25 days for treatment she reported generalised itching. Cutaneous examination revealed vesiculo-bullous eruptions on chest and abdominal wall, hyperpigmented face and diffuse desqua- mation on the limbs. All anti tuberculosis drugs were stopped and patient was put on local corticosteroid therapy for two weeks. The lesions cleared completely. Because of its low risk of entraining skin side effect, ethambutol was introduced the first drug in a dose of 750 mg. 24 hours later this provocation test, generalised itching and erythematovascular skin eruptions more marked on the extremities were appeared, further administration of ethambutol was stopped. Patch tests will be programmed when lesions disappeared.

Clinician should be alerted to consider ethambutol also as one of possible drug causing cutaneous eruptions.

P4413 Research on in vitro release kinetics of isoniazid (IZN) and omeprazole from oral tablets
Magda Costin 1, Bogdan Cioroiu2, Elena Butnaru 3, Holger Rüssmann2, Nicolas Schönfeld 1, Torsten T. Bauer1.

Introduction: The study aimed to follow the in vitro release kinetics of IZN and omeprazole, the influence of applied methods and release evaluation when associated with other antituberculous drugs.

Materials and method: As research method on the in vitro release of IZN and omeprazole it has been used the method of resistance in acid environment and dissolution method in neutral media. In order to evaluate the resistance in acidic conditions, 6 samples were taken in the time interval 5–110 minutes, while for dissolution in neutral media evaluation 11 samples were collected in the time interval from 10 to 320 minutes.

Results: Solubilization in acidic media: For IZN it was found a release degree of 85.9% at 5 minute and of 88.7% at 110 minutes. When associated with omeprazole, the maximum release degree it was identified at 30 minutes of 95.1%; when associated with Rifampicin, rifapentine, or other antituberculous drugs, the maximum release degree was found at 15 minutes of 99.6%. We found a very low release degree for omeprazole; the first concentrations being detected after 75 minutes and after 110 minutes we found a release degree of only 8.1%. Solubilization in neutral conditions: the lack of any IZN traces reveals that complete dissolution took place in acidic media, while for omeprazole it was found a 5.8% release degree at 10 minutes and of 40.2% after 320 minutes.

Conclusion: IZN shows a sensitive release pattern in the presence of antituberculous drugs and a slightly sensitive release pattern in the presence of omeprazole

Instead, omeprazole shows a very low release pattern when associated with IZN or other antituberculous drugs, which could cause modifications of the plasma concentrations.

P4414 Influence of inhaled bronchodilator therapy on bacterioexcretion and LQ in patients with lung TB with concomitant broncho-obstructive syndrome
Oana Kukla1, Evgeny Shmelev2. 1Granulematosis Lung Disease Department, 2Granulematosis Lung Disease Department, Central TB Research Institute RAMS, Moscow, Russian Federation

Aims: To evaluate the influence of bronchodilator therapy on bacterioexcretion and LQ in patients with lung TB and concomitant broncho-obstructive syndrome

We examined 123 patients with pulmonary TB, 47 of which had infiltrative form (IFTB), 42 patients had fibrocavernous form of pulmonary TB (FCBT), in 33 cases residual post-TB pulmonary sclerosis (PPS) was diagnosed. In 65 cases we used bronchodilator therapy with inhaled M-cholinolyltics and LABA (study group), rest of patients received theophylline per os (control group). All TB patients were treated with chemotherapy according WHO recommendations, excluding patients with PPS, in these cases no any chemotherapy was prescribed. Bacterioexcretion was assessed at the study start point, and after that it was controlled monthly till the 3rd month of therapy, this parameter was shown as a percentage of positive cases among the whole cohort of patients.

LQ evaluated at start and finish the study process using SGRQ questionnaire. We determined that bronchodilator usage accelerated rates of sputum clearance in IFTB patients on 16.8%, in FCTB patients – on 14.8%. The most dynamic data were obtained in IFTB patients. LQ in study group for IFTB patients improved at 35.6%, in control group – on 5.7%. Symptoms’ scale diminished up to 32%, “daily activity” improved for 35%, and “impact” scale of SGRQ for study group fell down up to 19.7%.

Conclusion: Modern bronchodilator therapy can accelerate the rate of sputum clearance due to drainage bronchial function and due to diminishing the ability for concomitant infection to arise, in the same time improving LQ of such patients greatly.

P4415 In vitro susceptibility of M. avium against protonamidine
Timo Weiss1, Tarek Sabha1, Jens Kollmeyer1, Torsten Blum1, Harald Mauch1, Holger Russmann2, Nicolas Schönfeld1, Torsten T. Bauer1. 1Dept of Pneumonology, Langenbeklinik Heckeshorn, 2Institute of Microbiology, Helios Klinikum Emil von Behring, Berlin, Germany

Introduction: M. avium is a potentially pathogenic mycobacterial species to humans, which is classified as difficult to cure. By the American Thoracic Society resistance testing in vitro in the case of newly diagnosed mycobacteriosis is recommended only for clarithromycin, but with treatment failure is shown the option for further testing. No data were so far reported for the susceptibility of M. avium to protonamid in vitro in the literature.

Methods: All M. avium strains that could be isolated from clinical materials in our laboratory from Jan 1st 2008 to May 31st 2010, were subjected to susceptibility testing on solid media according to DIN 58943-1.

Results: Out of 67 strains only one turned out to be resistant at an inhibitory concentration of 5 micrograms/ml protonamid. While only one further strain showed resistance to clarithromycin (32 mcg/ml), 18 strains showed resistance to moxifloxacin (4 mcg/ml).

Conclusions: Despite the absence of clinical treatment studies protonamid should be considered as a treatment option for mycobacteriosis by M. avium in the case of treatment failure or intolerance of a drug of first-line therapy.

P4416 Susceptibility of mycobacterium avium complex and mycobacterium xenopi to rifampin, rifapentine, clarithromycin and moxifloxacin, alone or in combination with ethambutol
Claire Andrejaj, Deepak Almeida, Eric Nuerberger, Jacques Grosset. Center for TB Research, Johns Hopkins University, Baltimore, MD, United States

Background: Pulmonary disease due to M. avium complex (MAC), and M. xenopi (Mx) is a growing health problem in industrialized countries and the optimal antibiotic treatment is still debated. We conducted in a vitro study to evaluate the susceptibility of the main antibiotics on MAC and Mx.

Methods: For MAC strain 101 and Mx ATCC strain 700898, minimal inhibitory concentrations (MICs), of clarithromycin (CLA), moxifloxacin (MFX), rifapentine (RPT), ethambutol (EMB) were determined on 7H11 media. Inoculum was 2.7 log10 CFU of Mx and 4.5 log10 CFU of MAC. Plates were read after 28 days of incubation at 37°C (MAC) or 42°C (Mx). MIC was defined as the lowest drug concentration that inhibits ≥99% of colonies compared to control. Combinations of EMB-RIF, EMB-RPT, MFX-CLA and EMB-MFX for Mx and MAC were tested using the checkerboard method.

Results: For MAC, MIC was >4 for CLA, 2 for MFX, >16 for RIF, >4 for RPT, 16 for EMB. For Mx, MIC was >4 for CLA, 2 for MFX, >16 for RIF, 4 for RPT, 16 for EMB. For both MAC and Mx, MIC was 1 for CLA when we
used Mueller Hinton media (pH=7.3 for Mueller Hinton media vs pH=6.6 for 7H11). Synergy was observed for EMB-RIF; EMB-MXF; MXF-CLA against Mx, and for EMB-RPT against both Mx and MAC. An additive effect was found for CLA-MXF, EMB-RIF, EMB-MXF against MAC.

**Conclusion:** The addition of EMB decreased the MIC of RPT against both MAC and Mx and decreased MIC of MXF and RIF against Mx. So, EMB could increase the in vivo activity of these antibiotics against these mycobacterial opportunistic pathogens. No antagonism between MXF and CLA was found.

### P4417
**In vitro susceptibility of mycobacterium bovis against moxifloxacin**

**Timo Weiss**, 1 Torsten Blum 1, Jens Kollmeier 1, Harald Munch 1, Holger Russmann 1, Nicolas Schönfeld 1, Torsten T. Bauer 1

1 *Dept. of Pneumology, Langenklinik Heckeshorn, Institute of Microbiology, Helios Klinikum Emil von Behring, Berlin, Germany*

**Introduction:** Mycobacterium bovis causative bovine tuberculosis is also responsible for diseases in humans. To date there are no data available on the in vitro susceptibility of M. bovis strains to moxifloxacin, an established second line drug in the treatment of disease caused by M. tuberculosis.

**Methods:** From M. bovis-positive cultures from BAL, sputum, pleural effusion or cerebrospinal fluid of 34 pts from the years 1993-2010, we retrospectively evaluated the sensitivity in vitro and the minimum inhibitory concentrations of moxifloxacin. Culturing and resistance testing was performed on solid Middlebrook agar plates.

**Results:** Out of 34 tested M. bovis-positive cultures 33 showed a sensitivity to moxifloxacin at 2 or 4 mcg/ml. Only one strain showed resistance.

**Conclusion:** Our study of a small group of patients shows a high sensitivity rate of moxifloxacin against M. bovis strains. Despite the absence of clinical treatment studies, we see a potential use of moxifloxacin as a second line drug, with regular ineffectiveness of the first-line drug pyrazinamide in M. bovis.

### P4419
**Improvement of the survival of lung cancer in a French monocentric cohort between 1990 and 2010**


**Background:** Authors report analysis of monocentric cohort of 1400 patients with lung cancer followed between 01.01.1990 and 31.12.2009.

**Methods:** Kaplan-Meyer and Foucher methods are used.

**Results:** The survival with Kaplan-Meyer method is 56% at 1 year, 23% at 5 years and 17% at 10 years. Analysis of relative survival, taking into account the mortality of the general population without lung cancer is 57% at 1 year, 26% at 5 years and 22% at 10 years (Method of Foucher, on 1990-2005 population).

<table>
<thead>
<tr>
<th>Relative survival at 1 year</th>
<th>Relative survival at 5 years</th>
<th>Relative survival at 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>94%</td>
<td>76%</td>
</tr>
<tr>
<td>Stage II</td>
<td>71%</td>
<td>51%</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>56%</td>
<td>22%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>34%</td>
<td>6%</td>
</tr>
</tbody>
</table>

The period analysis shows an improvement on overall relative survival.

<table>
<thead>
<tr>
<th>Relative survival at 1 year</th>
<th>Relative survival at 5 years</th>
<th>Relative survival at 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1994</td>
<td>50%</td>
<td>16%</td>
</tr>
<tr>
<td>1995-1999</td>
<td>59%</td>
<td>27%</td>
</tr>
<tr>
<td>2000-2004</td>
<td>59%</td>
<td>30%</td>
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<tr>
<td>2005-2010</td>
<td>ND</td>
<td>ND</td>
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</table>

The period analysis shows an improvement in relative survival at 5 years by stage.

<table>
<thead>
<tr>
<th>Survival at 5 years</th>
<th>1990-4</th>
<th>1995-9</th>
<th>2000-04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>57%</td>
<td>65%</td>
<td>64%</td>
</tr>
<tr>
<td>Stage II</td>
<td>37%</td>
<td>28%</td>
<td>47%</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>8%</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>7%</td>
<td>8%</td>
<td>26%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0%</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Conclusion:** This analysis shows a very interesting increase of the relative survival of lung cancer patients since 1990, global and by stage (1997 WHO Classification).

Best staging by PET and RMI and best medical strategies explain this results, specially for Stage III and Stage IV. An Hope for this pathology.

### P4420
**Survival outcomes of non small cell lung cancer (NSCLC) patients who are suitable for radical treatment at initial presentation**

**Masood Ahmad Khalil**, Joyce Barclay, *Respiratory Unit, The Royal Oldham Hospital, The Pennine Acute Hospitals NHS Trust, Oldham, Greater Manchester, Lancashire, United Kingdom*

**Background:** Lung cancer survival continues to remain poor despite the availability of better diagnostic & management strategies; as most patients have advanced disease at presentation with poor performance status (PS) & coexisting morbidities. All patients with limited disease bulk & good PS should be offered radical treatment to improve overall outcomes.

**Aims:** To assess the number of NSCLC patients who were suitable for treatment & determine the reasons for either not receiving or completing treatment. To compare outcomes of those who completed treatment with those who did not.

**Methods:** Retrospective study of all (136) newly diagnosed NSCLC (Jun 2008-Aug 2009). 9 were excluded (insufficient data).

**Results:** Of the 127 patients, 93% aged >/= 60, 52% females, 95 were not suitable and 32 were suitable for treatment. 28 received treatment (8 surgical resection, 8 radical radiotherapy, 12 chemo-radiotherapy) and 4 either did not receive or complete treatment (1 refused treatment, 1 deteriorated while receiving radical radiotherapy, 1 recurrent chest infections with deterioration, 1 treatment related side effects).

**Conclusion:** Although, carefully selected patients who received treatment showed however, these mean results hide significant variation across the cancer networks, which persists even after adjustment for case-mix (age, sex, stage, performance status, socio-economic status). The example of surgery for NSCLC is shown in the figure.

**Conclusions:** The results suggest that care for lung cancer patients in the UK is slowly improving, although some of the apparent improvement is likely to reflect the rise in data quality. However, wide variations in outcomes persist between organisations which is not explained by simple case-mix variation. These variations need to be the focus of on-going service improvement work.

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**437. Quality management for lung cancer patients**

**P4418**

**The National Lung Cancer Audit – Year 5 completeness and outcomes and case-mix adjustment**

**Paul Beckert**, 1 Roz Stanley 2, Ian Woolhouse 1, Laila Tata 1, Michael Peake 1, 1 Clinical Effectiveness and Evaluation Unit, Royal College of Physicians, London, United Kingdom; 2 Information Centre for Health and Social Care, NHS, Leeds, United Kingdom

**Introduction:** The National Lung Cancer Audit aims to record outcomes in lung cancer on a large scale and through case-mix adjustment, start to explain the wide variations in outcomes between hospitals in the UK and between the UK and other westernised countries. This abstract presents results for patients first seen in 2009 in England and Wales.

**Results:** For patients first seen in 2009, 37,304 cases were submitted from England (30,096), Wales (1,973), Scotland (4,379), Northern Ireland (819) and Jersey (37), representing >97% of the expected number of cases. Results suggest that the quality of care is improving.

**Headline results**

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed Histological diagnosis</td>
<td>68%</td>
<td>76%</td>
</tr>
<tr>
<td>Any anti-cancer treatment</td>
<td>45%</td>
<td>59%</td>
</tr>
<tr>
<td>Overall surgical resection rate</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>

|                  |
| Odds Ratio for Surgery in NSCLC by Network |

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**Tuesday, September 27th 2011**
P4421
Survival outcomes in advance non-small cell lung cancer – A developing country scenario
Randeep Guleria, Anant Mohan, Sachin Kumar, Ashraf Ali, Ajeet Kumar.
Medicine, All India Institute of Medical Sciences, Delhi, India

Background: Lung cancer is common and has poor survival outcome. Chemotherapy provides modest improvement. Many patients can not afford chemotherapy and it utility in advanced lung cancer in resource limited setting is debatable. Our goal was to assess the effect of chemotherapy on survival.

Method: 78 cases with advanced Non Small Cell Lung Cancer were followed up. All cases were offered platinum based chemotherapy. Patient characteristics, staging and performance status was noted. Chemotherapy arm was compared with the group not willing for chemotherapy for mortality and other parameters. Relevant statistical analysis was done. Kaplan-Meir survival estimates was generated.

Results: 41 patients received chemotherapy and 37 patients did not receive chemotherapy. The 2 groups were well matched.

Table 1
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemotherapy (n=41)</th>
<th>Not on chemotherapy (n=37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>55.6±10.7</td>
<td>58.3±10.6</td>
<td>0.237</td>
</tr>
<tr>
<td>BMI, mean (kg/m²)</td>
<td>20.7±5.5</td>
<td>19.2±3.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage, 3 (%)</td>
<td>19 (46.3%)</td>
<td>15 (40.5%)</td>
<td>0.653</td>
</tr>
<tr>
<td>Stage, 4 (%)</td>
<td>22 (53.7%)</td>
<td>22 (59.5%)</td>
<td>0.663</td>
</tr>
<tr>
<td>ECOG, 1 (%)</td>
<td>18 (43.9%)</td>
<td>14 (37.8%)</td>
<td>0.256</td>
</tr>
<tr>
<td>ECOG, 2 (%)</td>
<td>21 (51.2%)</td>
<td>17 (45.9%)</td>
<td>0.256</td>
</tr>
<tr>
<td>ECOG, 3 (%)</td>
<td>2 (4.9%)</td>
<td>6 (16.2%)</td>
<td>0.256</td>
</tr>
<tr>
<td>Median Survival, days (95% CI)</td>
<td>285 (209-360)</td>
<td>118 (74-161)</td>
<td>0.028</td>
</tr>
<tr>
<td>6 months survival (%)</td>
<td>52%</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Results of Kaplan-Meir analysis are shown.

Conclusion: In advanced lung cancer patients a platinum based chemotherapy provided a significant survival advantage and should be advised to these patients even in a resource limited setting.

P4422
The role of chemotherapy re-challenge in non small cell lung cancer. A retrospective study in a tertiary general hospital and thoracic center
Oncology Unit, 3rd Department of Athens Medical School, General and Chest Diseases Hospital Sotiria, Athens, Greece

Background: Chemotherapy re-challenge (CTR) is an established clinical approach in many malignancies such as ovarian cancer and small cell lung cancer.

Aims and methods: We screened medical records of 2160 patients (pts) diagnosed with NSCLC and treated with chemotherapy (CT) at our institution, between January 2003 and February 2011.

Results: 102160 pts (0.46%) were offered a CTR regimen. The histological subtypes were adenocarcinoma (A) (5 pts), squamous cell carcinoma (3 pts) and not specified (NS) (2 pts). All patients were of good Performance Status (0-1), and the majority without any comorbidities (7/10). All pts were treated with a platinum agent combined with either pemetrexed (6 pts), taxane (3 pts) or gemcitabine (1 pt). 3/10 pts had initially received adjuvant CT and CTR on their first relapse, whereas 7 pts were initially treated for advanced/metastatic disease. In the later 7 pts, partial response (PR) as best response was observed in 6 (68.7%). Median time to progression (TTP) after the initial CT was 9.8 months (range 3.6-37.5). Best responses following CTR were PR in 2 (20%), stable disease (SD) in 2 (20%) and disease progression (PD) in 4 (40%), with 2 pts still on treatment. Median TTP after CTR was 3 months (2.5-12). The 2 pts with PR after CTR (1 A, 1 NS) were both treated with platinum-pemetrexed combination and had both demonstrated PR after the initial CT and TTP of 9 and 17 mo respectively.

Conclusions: CTR is rarely opted in NSCLC likely due to rapid disease progression. The role of CTR is limited and rather unsuccessful. Nevertheless, selected patients might benefit from this approach.

P4423
Curtative treatment vs. best supportive care in advanced non small cell lung cancer patients in aged person
Junghyun Chang, Jihye Kim, Youdu Ryu, Jinhwa Lee, Soonwo Kim. Internal Medicine, Ewha Womans University, Seoul, Republic of Korea

Rationale: With the introduction of new chemotherapeutics showing better efficacy and manageable toxicity, it is now well established the role of palliative chemotherapy in advanced NSCLC. Although the majority of patients benefit from systemic anticancer treatment, including chemotherapy and/or radiation therapy of curative aim had a survival benefit comparing to best supportive care (BSC) especially in aged advanced lung cancer subjects.

Methods: The data was retrieved retrospectively from medical records of 618 patients who had been diagnosed as non-small cell lung cancer (NSCLC) in tertiary university hospital from 2000 through 2007. The analysis was confined to 146 subjects of stage IIIB or IV NSCLC over 70 years old.

Results: The mean age at diagnosis was 77 years old (range: 70-95). In good performance group (ECOG, 0-1) was 109 patients (75%) and bad performance group (ECOG, 2-3) was 37 (25%). The mean survival time following the diagnosis was 10.0±12.8 months (m). As compared to BSC (n=92), the curative treatment (CT) group (n=54) showed the better survival rate (CT median 7.6±9 m, 95% confidence interval (CI): 5.2-8.8 vs. BSC median 4.0±8.0 m, 95% CI: 2.3-5.7. p<0.008). Within good performance group, the better survival rate was also shown in curative treatment group than BSC. Contrarily, within bad performance group, there was no significant survival gain in curative treatment over BSC.

Conclusions: In over 70 years old, the survival benefit was observed in curative treatment, especially in good performance status, compared to best supportive care. In relatively poor performance status, although the outcome of survival time had a little superior tendency in curative treatment, meticulous attention should be given in treatment decision.

P4424
Assessment of German national lung cancer guideline quality indicators in routine practice – Does the new TNM-system make a difference?
Torsten Blum, Jens Kollmeier, Nicolas Schönfeld, Win Aumüller, Sandra Delis, Wolfram Grünig, Wielke Nehls, Torsten T. Bauer. Department of Pneumology, Pulmonary Diseases Clinic Heckeshorn, HELIOS Klinikum Emil von Behring, Berlin, Germany

Background: Quality assurance is an essential tool for assessing and optimizing quality of care. For that purpose, the German national lung cancer guideline (GL), published in 2010, has defined nine quality indicators (QI). So far, neither these QI have been prospectively evaluated, nor corresponding reference intervals have been specified. Furthermore, no evidence exists for the practicability of the QI concerning the utilization of the new TNM-system (UICC 7).

Methods: All patients with a first diagnosis of lung cancer (FD), admitted to our lung cancer centre between 01.01.2008 and 31.12.2009, were included into this study. Data collection has been performed prospectively using our tumour documentation system (TDS) and hospital information system (HIS). In a retrospective analysis two groups were defined in which the patients were staged by the old UICC 6 (FD in 2008) and the new UICC 7 (FD in 2009) staging system, respectively.

Results: Patients’ characteristics were similar in both groups (2008: 595 pt.; 2009: 641 pt.). For 7 out of 9 QI a result could be determined according to the defaults published in 2010, has defined nine quality indicators (QI). So far, neither these QI have been prospectively evaluated, nor corresponding reference intervals have been specified. Furthermore, no evidence exists for the practicability of the QI concerning the utilization of the new TNM-system (UICC 7).

Conclusions: In this study we were able to completely assess 7 out of 9 QI proposed by the GL exclusively on the basis of routine data of our TDS and KIS.

TUESDAY, SEPTEMBER 27TH 2011

815s
These data will not only help to improve the quality of care in our lung cancer centre but also allow first conclusions on the undetermined reference intervals for the GL-QI. However, the GL-QI should be further evaluated within a prospective, multicentre study.

**P4425**

**Outcome of patients discharged from rapid access lung clinic (RALC) with non cancer diagnosis:** Five year follow up

Andrew Wright, R. Sarkar, Lorraine Creech, Robert Stead, Marta Baboeres.

Respiratory Medicine, Macclesfield District General Hospital, Macclesfield, Cheshire, United Kingdom

**Introduction:** Since publication of NICE guidelines in 2000 RALC has become standard practice. These clinics target service towards diagnosis of lung cancer, with streamlined investigation and MDT discussion. We set up our RALC in 2003.

**Aim:** To assess if patients discharged from RALC without a diagnosis of cancer had received adequate care and were not re-presenting with malignancy.

**Methods:** We analysed a random selection of patients discharged from RALC with a non-cancer diagnosis.

Data collected: investigations, duration of follow-up, diagnosis on discharge and 5 year outcome

**Results:** A total of 220 patients were discharged during the study period from or RALC without a diagnosis of lung cancer and 35 were analysed. Male: 28. Average (SD) age 63 (14). CT scan was done in 43 patients (78%) and bronchoscopy in 20 (36%). All the cases were discussed at MDT. 30% of patients were discharged from RALC with 70% discharged to respiratory unit patient follow-up. Main diagnoses on discharge were: infection (38%), COPD (15%), benign nodules/plaques (10%), interstitial lung disease (7%), bronchiectasis (7%), vascular (7%), others (15%).

Median (range) follow-up in RALC was 24 (0-700) days. 14 (25%) patients died over the 5 years, with average age when first seen of 76 (range 61-86). Cause of death was: non respiratory malignancy (5), cardiac disease (3) and infective causes (6). None of these deaths was related to initial presentation to RALC. No patients developed lung cancer over the duration of study.

**Conclusion:** Our five year follow up study shows that streamlined investigations and MDT input in RALC is effective in ruling out lung cancer.

**P4426**

Reducing unscheduled attendances at hospital due to lung cancer via a rapid access flexible clinic

Hannah Morgan, Luke Hodgson, Richard Lee, Sarah Doffman. Dept of Respiratory Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom

Brighton and Sussex University Hospitals (BSUH) comprises two acute hospitals in SE England. The lung cancer MDT sees 250 new cases/year. Regional and UK outcomes have been historically poor for 1 & 5 year survival with high numbers presenting late.

Data suggests that lung cancer had the highest rate of unscheduled admissions & the greatest number of inpatient bed days compared with other cancer sites in the Trust.

We present a review of admissions in 2010, including stage at presentation/route to diagnosis and the impact of introducing a flexible clinic through which patients with a known diagnosis can self- trigger an appointment or rearrange their existing appointment.

During 2010 there were 110 patients admitted as an unscheduled emergency, 83 (75%) through A&E. 33 patients (30%) were newly diagnosed and of those 26 patients (24%) had metastatic disease at presentation (Stage IV).

Within the flexible clinic 22 patients triggered an appointment and thereby avoiding an emergency unscheduled admission. There was a 20% reduction overall in lung cancer admissions in 2010 compared with 2008/9. 107 clinic appointments were cancelled following a telephone contact with the patient facilitating capacity for rapid access referrals: 96 of these were cancelled as the patients were asymptomatic.

**Conclusions:** 1. Introduction of the flexible clinic has reduced overall admissions by 20%. 2. A high proportion of patients were diagnosed with advanced disease whilst an inpatient. 3. Greater awareness of the symptoms of lung cancer may reduce late presentation. 4. Greater uptake of the flexible clinic may further reduce unscheduled admissions with lung cancer.

**P4427**

Fast track lung cancer service in a tertiary care centre

R. Naseer, M.E.J. Callister, P.K. Plant. Respiratory Medicine, St. James University Hospital, Leeds, Yorkshire, United Kingdom

**Background:** Leeds is one of the largest Lung Cancer Centres in the UK

**Aim:** Audit our practice against Department of Health (DoH) & local standards.

**Methods:** Retrospective audit of patients (pts) referred to the Fast Track cancer clinic from 03.10 to 04.10.

**Results:** 153 pts attended. 51% were fast track referrals (CO2). 37% were diagnosed with lung cancer with which 32% received best support care, 12% had radical surgery & 51% had oncological treatment. 50% had a benign diagnosis, 8% were enrolled into monitoring. 8 pts breached the 62 day target of which 63% required more than 1 diagnostic test. Analysis of breaches identified 29% surgical delays & 35% radiological delays (CT biopsy &/or PET).

**Conclusion:** 14 day & 31 day targets are achieved, however to achieve the 62 day target requires close liaison between specialties and pts requiring tests delivered by non pulmonologists are more likely to breach.

**P4428**

Rapid access lung cancer clinic – A patient satisfaction survey

R. Mustafa, S. Naik, J. Mills, M. Munavvar. Respiratory Medicine, Lancashire Teaching Hospitals, Royal Preston Hospital, Preston, Lancashire, United Kingdom

**Background:** Royal Preston Hospital runs a rapid access lung clinic for efficient staging of suspected lung cancer patients. Staging CT-scans and discussion with chest radiologists for planning and scheduling the investigations for definitive staging is carried out at first attendance. Moreover management plans are discussed with patients by doctors and reinforced by dedicated lung cancer nurse specialists who also provide ongoing psychological support to suspected cancer patients at first appointment.

**Aim:** To ascertain if patients were satisfied with the service offered at the rapid access clinic and if this service lead to early diagnostic/r staging investigations as promised. We also wanted to identify areas which needed further development and assess the different support that was particularly well liked by our patients.

**Methods:** Survey questionnaires were posted to 35 patients attending the rapid access lung cancer clinic between January 2010 and February 2010.

**Results:** 42% (n=15) of patients returned the questionnaires.

**Abstract P4427 – Table 1. Summary of results**

<table>
<thead>
<tr>
<th></th>
<th>CO2 (days)</th>
<th>Non CO2 (days)</th>
<th>Unit Target</th>
<th>DoH Target</th>
<th>Target achieved – CO2 (%)</th>
<th>Target achieved – Non CO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to 1st outpatient appointment (OPA)</td>
<td>7 (1–14)</td>
<td>8 (1–33)</td>
<td>7 days</td>
<td>14 days</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CT prior to Bronchoscopy</td>
<td>n/a</td>
<td>n/a</td>
<td>7 days</td>
<td>14 days</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Sampling to pathology</td>
<td>5 (1–18)</td>
<td>7 (3–15)</td>
<td>n/a</td>
<td>7 days</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PET prior to radical treatment</td>
<td>n/a</td>
<td>n/a</td>
<td>7 days</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Triage to OPA Oncology (Onco, Surgery (Surg)</td>
<td>17 (1–100)</td>
<td>29 (1–50)</td>
<td>3 days</td>
<td>100</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Decision to treat to 1st treatment</td>
<td>21.5 (4–28)</td>
<td>12.5 (0–31)</td>
<td>31 days</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Initial referral to 1st definitive treatment</td>
<td>46 (6–116)</td>
<td>n/a</td>
<td>62 days</td>
<td>81</td>
<td>83</td>
<td>83</td>
</tr>
</tbody>
</table>
**P4429**

How do patient and hospital features influence outcomes in small cell lung cancer in England? 1,2

Annasulochana Lall, 1 Tatia 1, Catherine Free2, Rosamund Stanley3, Michael Peake2, David Baldwin2, Richard Hubbard1, 2 Epidemiology and Public Health, 1Nottingham University, Nottingham, United Kingdom; 2Glennfield Hospital, University Hospitals of Leicester, Leicester, United Kingdom; 3The NHS Information Centre, NHS, Leeds, United Kingdom; 4Respiratory Medicine, City Campus, Nottingham University Hospitals, Nottingham, United Kingdom

**Introduction:** There is geographical variation in the delivery of active treatment in lung cancer. We wanted to find out whether the features of patients and/or NHS Trusts influence this variation.

**Methods:** We linked the National Lung Cancer Audit and Hospital Episode Statistics and used multiple logistic and Cox regression analyses to assess the influence of patient and NHS Trust features on small cell lung cancer outcomes.

**Results:** There were 87,252 patients, of which 7,845 had histologically proven small cell lung cancer and 4820 (61%) received chemotherapy. Increasing age, worsening performance status, extensive stage and greater co-morbidity all significantly reduced the likelihood of receiving chemotherapy. Patients first seen in a "good" trial centre (defined as those entering >5% of expected patients into clinical trials) were 42% more likely to receive chemotherapy than those seen in other centres (adjusted OR 1.42, 95% CI 1.06, 1.90).

**Conclusion:** Overall survival was lower in men, and as age, performance status, stage and co-morbidity increased prognosis worsened. Chemotherapy led to a 50% reduction in the likelihood of death (adjusted HR 0.48, 95% CI 0.42, 0.55), and in those patients who received chemotherapy, overall survival was not affected by whether they were seen in a "good" centre.

**P4430**

A retrospective analysis of patient presentation to primary and secondary care prior to subsequent late stage lung cancer diagnosis

Anand Shah1, Sue Teoh1, Ibipinder Mann1, 2Respiratory Medicine, North West London Hospitals Trust, London, United Kingdom; 2Respiratory Medicine, West Middlesex University Hospital Trust, London, United Kingdom

**Introduction:** Lung cancer causes significant mortality representing over 20 per cent of cancer death in 2008 in the UK. This is largely due to the high percentage of late stage disease at presentation and low proportion of radical treatment. We report on the primary and secondary care presentation in patients subsequently diagnosed with late stage (3 or 4) lung cancer.

**Method:** All patients with stage 3 or 4 lung cancer diagnosed in 2008 were included. Primary care, A&E and secondary care presentation were retrospectively analysed prior to lung cancer diagnosis. Symptom presentation was assessed using NICE lung cancer referral guidelines as a gold-standard.

**Results:** 70 patients were identified during the study period. Primary care information was available in 38 patients. 34 percent of patients were diagnosed following an emergency secondary care presentation. 40 patients presented to health professionals prior to their emergency presentation or lung cancer referral with symptoms fulfilling NICE criteria for lung cancer specialist referral with 9 weeks from referral/presentation being the average. Where primary and secondary care information was available, 21 percent of patients did not see a health care professional till emergency presentation or referral. Average length of symptoms of patients prior to presentation/referral was 12 weeks.

**Conclusion:** Our study shows there is considerable delay in specialist referral from health professionals altogether considerable delay in patient presentation. This suggests further lung cancer awareness is required amongst at-risk patient populations as well as primary and secondary health care providers.

**P4431**

General practitioner (GP) communication with potential lung cancer patients: review of practices prior to onward secondary care referral

Selva Selvaraj, Kate Garbett, Julia McAdam, Kottalai Sinivasan, Harmesh Meudgil. Respiratory Medicine, Princess Royal Hospital, Telford, United Kingdom; 2Respiratory Medicine, University of Keele Medical School, Keele, United Kingdom

**Background:** Anecdotally, there is heterogeneity in what patients understand as "red light" symptoms of lung cancer and how these are communicated. This is partly because of accelerated referral pathways after initial abnormal radiology and potentially bypassing direct contact in primary care.

**Aim:** To identify if and how GPs are communicating red light symptoms and report (1) how and what patients are told prior to attending secondary care clinics, (2) how these findings relate to subsequent outcomes, and (3) the performance status of patients at the point of initial referral.

**Results:** Over a 4 month period to August 2010, of 107 referrals, 95 (89%) had complete data available for analysis. Mean (range) age was 65.8 (29-95) years. 54% are male. 79/95 (83%) had prior information from their GP with no home consultations, 15 (19%) had been contacted by telephone, 4 (5%) had received letter, and 60 (76%) had attended the GP surgery. 8 (10%) had been told that they had a possible or definite lung cancer, 54 (68%) had been told they had abnormal chest x-ray findings, and 17 (22%) had been told they were being referred for investigation. Performance status was, respectively from 0 to 4, 36 (38%), 34 (36%), 18 (19%), 6 (6%), and 1 (1%).

**Conclusions:** Results confirm the variation in referral routes and methods as well as the wide age range referred under this urgent system, but with only 23 (24%) patients with an eventual outcome of lung cancer. Results further emphasize the need to balance any direct and early information from the GP priming the patient before subsequent consultation in secondary care.

**P4432**

Does raising awareness of lung cancer symptoms in primary care alter referral patterns?

Ronan Astin1, Elizabeth Paddison2, Adam Woollf 1, Natalie Soobadou 1, Duncan Powrie 1, 2Respiratory Medicine, Southend University Hospital, Southend, Essex, United Kingdom; 3Service Res-Design and FPC Team, South East Essex Primary Care Trust, Southend, Essex, United Kingdom

**Background:** Patients with lung cancer often present late with advanced disease. This results from both symptomatic patients not presenting to primary care and delayed referral following presentation.

**Aim:** To examine whether sending General Practitioners (GPs) a reminder of the "red light" symptoms of lung cancer would increase urgent referrals and lead to earlier diagnosis.

**Method:** All 67 surgeries in South East Essex PCT received a postal reminder of the referral criteria for lung cancer. All suspected cancer referrals to Chest Clinic for 10 weeks before and after this were audited retrospectively and each case followed to completion on the pathway.

**Results:** 121 patients were referred over 20 weeks. The total number of referrals increased post intervention from 57 to 64 (12%) though this was not statistically significant (p=0.6). There was a statistically significant increase in referrals in the first 3 weeks post intervention (p=0.046) but this effect was lost by week 4 (p=0.2). More patients were discharged from the pathway in the post intervention group (28.1% vs 24.6%, p=0.2) and fewer diagnosed with cancer (26.6% vs 28.1%, p=0.2). Referrals due to haemoptysis increased in the post intervention group (10% vs 5.2%) but this did not reach significance (p=0.06).

**Conclusion:** Sending out referral guidelines resulted in an initial increase in referral numbers. This effect was lost after 3 weeks and did not improve cancer detection rates however numbers in this study were small. This suggests that conscious efforts need to be focussed on increasing patient as well as GP awareness if outcomes are to improve.

**P4433**

Outcome of lung cancer alerts in chest X-rays

Rahileddin Sarkar, Masooma Safary, Jahnavi Samanuru, Niall O’Reilly, Ana de Ramón Casado. Respiratory Medicine, Warrington Hospital, Warrington, Cheshire, United Kingdom

**Background:** Appropriately communicated alert messages on suspicious chest x-rays (CXR) is an important cornerstone in diagnosing lung cancer early. It is a standard practice in our hospital for a suspicious CXR to be faxed to the requesting department after a consultation. We investigated the effectiveness of the aforesaid system.

**Method:** Retrospective analysis of the outcome of CXR alerts from 2008-10 using the hospital radiology, laboratory systems and clinic letters.

**Results:** Out of 387 alerts analysed [mean age (sd) 70 (13) years], 239 (62%) resulted in rapid access lung clinic referrals. Radiological follow up (fu) occurred in 90% (348) of which 163 (47%) were diagnosed to have cancer. CXR fu was done in 93% (after a median period of 3 weeks; inter-quartile range 1-5wks) and 298 (77%) had CT scan (after a medium gap of 3 wks; IQR 2-4wks). In 17 (4%), no identifiable reason could be found for no radiological fu. 5/17 patients (1.3% of all) were eventually found to have malignancy. We also measured the outcomes of different abnormality patterns in the initial CXR.

**Table 1**

<table>
<thead>
<tr>
<th>Opacity/consolidation</th>
<th>Effusion</th>
<th>Hilar mass</th>
<th>collapse</th>
<th>Pleural thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>316</td>
<td>36</td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>No. of cancer</td>
<td>140 (44%)</td>
<td>21 (58%)</td>
<td>43 (45%)</td>
<td>5 (39%)</td>
</tr>
<tr>
<td></td>
<td>13 (13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Nearly half the alerts resulted in cancer diagnosis. By distributing alert messages on suspicious CXR, radiology departments can expedite early diagnosis of lung ca. We also found out that pleural effusion, opacity/consolidation, hilar mass findings in the CXR had similar potential for eventually turning out to be malignant in the study population.
Conclusions: Despite earlier findings, a CT scan was not performed prior to FOB in all patients. Fewer FOBs occurred in 2010, and may be due to the selection of patients for endobronchial ultrasound. Non-diagnostic FOBs occurred in both periods, however, further reductions in unnecessary procedures may be achievable.

Methods: Patients with a final diagnosis of small cell (SCLC) or non-small cell (NSCLC) lung cancer over a 6-month period in 2010 and the equivalent period in 2008 were analysed. The timing of the CT scan and whether FOB resulted in a diagnosis from biopsy or cytology was recorded. CT scans were reviewed to assess whether a lesion was likely to be visible at FOB.

Results: 88 patients (mean (SD) age 69 (11) years) with SCLC (n=13) and NSCLC (n=75) were identified in 2010. All underwent a CT scan. 32% of patients underwent FOB (60% in 2008). CT scanning was performed prior to bronchoscopy in 86% of patients (68% in 2008). Non-diagnostic FOBs remained common (48% in 2010, 35% in 2008). CT scans indicating endobronchial disease were associated with a positive likelihood ratio of 2.6 (2.8 in 2008). 62% of non-diagnostic procedures were predictable from the CT scan (67% in 2008).

Background: Management of patients with SPNs depends critically on the pre-test probability of malignancy. There are currently two clinical predictions models for SPNs based on data from North America. However, these models have not been validated in UK patients, in particular those managed by a Lung MDT.

Objective: To validate the two existing prediction models in patients with SPNs managed by the Lung MDT at a large teaching hospital.

Methods: 175 patients with SPNs measuring 8–30 mm managed by the Lung MDT over 3 years (2007-2009) were identified retrospectively through the institutional Lung Cancer database. Data on age, smoking, cancer history, nodule size, location, speculation, and final diagnosis was collected. Each case’s final diagnosis was compared with the probability of malignancy predicted by two models: the Mayo Clinic model and the Veteran Affairs (VA) one. The accuracy of each model was assessed by calculating areas under the receiver operating characteristic (ROC) curve and the models were calibrated by comparing predicted and observed rates of malignancy.

Results: The area under the ROC curve for the Mayo model (0.832; 95% CI 0.753-0.911) was higher than that of the VA model (0.739; 95% CI 0.641-0.838). Calibration curves showed that both models slightly underestimated the probability of malignancy for patients across all deciles of predicted probabilities, except for those with highest probability of malignancy, where the VA model slightly overestimated probability.

Conclusions: The two existing prediction models are sufficiently accurate to guide management of patients with SPNs managed by a Lung MDT.

The value of immunohistochemical markers in the differential diagnosis of adenocarcinomas

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When differential diagnosis of adenocarcinoma in lung cannot be made, immunohistochemical staining may be necessary. Value of immunohistochemical staining in the differential diagnosis of adenocarcinomas was evaluated. 74 cases of different adenocarcinomas were enrolled. Pathology slides were stained with routine H&E staining and immunohistochemical markers. Positive CK7 immunostaining was seen in 100% of lung adenocarcinomas, papillary thyroid adenocarcinomas (PTC) and breast invasive ductal carcinomas (BIDC) and 15% of gastrointestinal (GI) adenocarcinomas, whereas none of prostate adenocarcinomas were positive. Positive CK20 immunostaining was seen in 75% of GI carcinomas and 10% of prostate adenocarcinomas whereas none of lung adenocarcinomas, BIDCs and PTCs showed positive CK20 immunostaining. TTF-1 staining was observed in 100% of PTCs, 83.3% of lung adenocarcinomas, 20% of BIDCs, 15% of GI carcinomas and 10% of prostate carcinomas. Positive p53 immunostaining was seen in 87.5% of lung adenocarcinomas, 85% of GI adenocarcinomas, 90% of PTCs and 80% of BIDCs. P53 staining wasn’t observed in prostate adenocarcinomas. CK7+CK20- staining panel’s sensitivity and specificity was found as 100% and 98% respectively in differential diagnosis of lung and GI adenocarcinoma. In differential diagnosis of lung adenocarcinomas from breast adenocarcinomas, TTF-1 marker had 83.3% sensitivity and 80% specificity. Consequently, immunohistochemical studies were found valuable in differential diagnosis of lung adenocarcinomas from other adenocarcinomas. Especially in patients with lung adenocarcinoma CK 7+CK20- staining pattern seem to give important contribution to differential diagnosis.
**Late-breaking abstract: Local and systemic distribution of the GATA-3-specific DNAzyme hgd40 after inhalative exposure**

Late-breaking abstract: Local and systemic distribution of the GATA-3-specific DNAzyme hgd40 after inhalative exposure. We developed the DNAzyme hgd40 which was shown to effectively target the specificity of DNA base pairing with an inherent RNA-cleaving enzymatic activity.

Introduction: The aim of this study was to investigate local and systemic distribution of hgd40 after local exposure in mice, rats and dogs.

Methods: Randomized double blinded placebo controlled trials and quality of life in patient with bronchiectasis

Bronchiectasis is an inflammatory airway disease with vicious cycle of infection and inflammation. Macrolides have been reported for improve clinical outcomes, we study the effects of macrolide on clinical outcomes such as symptom scores and quality of life in patient with bronchiectasis.

Material and methods: Randomized double blinded placebo controlled trials of roxithromycin 300 mg or placebo once daily for 8 weeks in patient with bronchiectasis.

Conclusion: Once daily roxithromycin showed benefit on clinical outcomes as well as quality of life. Larger studies of the effects of macrolide in bronchiectasis treatment with longer follow-up times should be done.

**Late-breaking abstract: Pre-clinical characterization of RP3128, a novel and potent CRAC channel inhibitor for the treatment of respiratory disorders**

Calcium release activated calcium channels inhibitors have a potent role in treatment of airway disorders. TNF-α, LTα, and mast cell degranulation are determined. Pre-clinical efficacy of RP5090 was confirmed in respiratory models of ovalbumin-induced chronic airway inflammation. Consistent with in vivo findings, the compound caused a significant inhibition of mast cell degranulation manifested by a reduction in histamine release.

Conclusions: Results demonstrate the therapeutic potential of RP5090 as an antiasthmatic agent as evidenced from pre-clinical data. Further biological profiling in respiratory models is planned in addition to toxicological evaluation prior to Phase 1 clinical trials.

**Late-breaking abstract: Pre-clinical efficacy of RP5090 in PI3Kδ mediated airway disorders**

Calcium release activated calcium channels inhibitors have a potent role in treatment of airway disorders. TNF-α, LTα, and mast cell degranulation are determined. Pre-clinical efficacy of RP5090 was confirmed in respiratory models of ovalbumin-induced chronic airway inflammation. Consistent with in vivo findings, the compound caused a significant inhibition of mast cell degranulation manifested by a reduction in histamine release.

Conclusions: Results demonstrate the therapeutic potential of RP5090 as an antiasthmatic agent as evidenced from pre-clinical data. Further biological profiling in respiratory models is planned in addition to toxicological evaluation prior to Phase 1 clinical trials.
are key features of COPD. We investigated the effects of NVA237, a once-daily (OD) inhaled long-acting muscarinic antagonist, on exercise endurance in pts with COPD.

Methods: 108 pts with moderate-to-severe COPD were randomized to a cross-over design of NVA237 50 or placebo OD for 3 weeks, with a 14-day washout. The primary outcome was endurance time during submaximal exercise tolerance test on Day 21 of treatment. Endurance time after first dose, dynamic hyperinflation (inspiratory capacity [IC] at isotime during exercise), and morning trough FEV1 were also measured.

Results: On Day 21, endurance time significantly increased by 21% with NVA237 compared with placebo; this effect was significant from Day 1, with an increase of 10% (Table). Dynamic IC at exercise isotime and trough FEV1, showed significant and clinically relevant improvements from Day 1 that were sustained throughout the study (Table).

The safety profile of NVA237 was similar to that of placebo.

Conclusion: NVA237 OD produced immediate and significant improvement in exercise endurance from Day 1, accompanied by sustained and significant improvements in IC at isotime and meaningful improvements in trough FEV1. Improvement in endurance time increased over the study period, suggesting that mechanisms beyond improved lung function play a role in enhanced exercise tolerance.

4498 Late-breaking abstract: Preclinical evaluation of an inhibitor of cytosolic phospholipase A2 for the treatment of asthma
Christopher Hewson1, Sheena Patil1, Luigino Calzetta2, Hinnah Campwala1, 5212372 effectively inhibited leukotriene B4, thromboxane A2 and PGD2 (IC50s 762372 OD produced immediate and significant improvement in

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The safety profile of NVA237 was similar to that of placebo.

4500 Late-breaking abstract: Serum concentrations of new factors (IL-20, galectin 3, IL-29 and IL-33) involved in angiogenesis in patients with advanced non-small cell lung cancer (NSCLC)
Wojciech Naumnik, Maria Ossolinska, Katarzyna Niewiarowska, Elżbieta Chyczewska, Department of Pulmonology, Medical University of Białystok, Białystok, Poland

There are several factors involved in angiogenesis, not tested yet, whose role is not clear in patients with lung cancer. Our pilot study was carried out to analyze the serum concentrations of IL-20, galectin 3, IL-29 and IL-33 (ELISA) in patients with non-small cell lung cancer (NSCLC) before chemotherapy, 15 sarcoidosis (BBS), 8 hyper-sensitivity pneumonitis (HP) and 15 healthy controls (H).

The serum concentration of IL-20 was highest in NSCLC, lower in H and lowest in HP (45,1±4,2 pg/ml; p=0,01). PF-5212372 was safe and clinically relevant improvements from Day 1 that were sustained throughout the study (Table).

The safety profile of NVA237 was similar to that of placebo.

Conclusion: NVA237 OD produced immediate and significant improvement in exercise endurance from Day 1, accompanied by sustained and significant improvements in IC at isotime and meaningful improvements in trough FEV1. Improvement in exercise endurance time increased over the study period, suggesting that mechanisms beyond improved lung function play a role in enhanced exercise tolerance.
Results: SELDI-TOF spectra of patients with lung cancer, healthy control and high risk are shown for the most discriminatory peaks of 11480 m/z, 11547 m/z and 11679 m/z.

Discriminatory proteomic features between lung cancers and healthy controls

<table>
<thead>
<tr>
<th>Proteomic feature (m/z)</th>
<th>p value</th>
<th>AUROC</th>
<th>Average intensity of lung cancer cases</th>
<th>Average intensity of healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>11480</td>
<td>3.12</td>
<td>0.88</td>
<td>1.24</td>
<td>–</td>
</tr>
<tr>
<td>11547</td>
<td>1.35</td>
<td>0.87</td>
<td>0.88</td>
<td>–</td>
</tr>
<tr>
<td>11679</td>
<td>4.87</td>
<td>0.87</td>
<td>1.03</td>
<td>–</td>
</tr>
</tbody>
</table>

These proteomic features were present in only lung cancer group, but not in healthy control or high risk groups.

Conclusion: SELDI-TOF-MS method can correctly distinguish patients with lung cancer from healthy individuals and SELDI-TOF-MS method may be a new tool in diagnosis and screening test for lung cancer.

4502
Bioconductance as adjunctive technique for evaluation of patients with lung masses detected by chest CT
Karleen Callahan, Rex Yung, Ming-Ying Zeng, Michael Garff. Clinical Affairs, FreshMedx Inc, Salt Lake City, UT; 1United States Medicine and Oncology, Div of Pulmonary Critical Care, Johns Hopkins University, Baltimore, MD, United States Medicine, Pulmonary & Critical Care Medicine, Johns Hopkins University, Baltimore, MD, United States

Introduction: CT screening may reduce LC mortality in high risk subjects but also finds many masses with indeterminate features resulting in invasive procedures for benign lesions.

Aims: We hypothesize that trans-thoracic bioelectrical conductance measurements may discriminate benign from malignant CT-detected lesions.

Methods: 41 subjects with CT-detected masses and or lung cancer symptoms such as cough, hoarseness, dyspnea, hemoptysis, weight loss or recurrent respiratory infections enrolled. Prior to biopsy, measured 9 parameters at 62 sites were conducted with Bioconductance Scan Platform (BSP). For each subject a composite score from collected data was calculated and an optimal cut-point set to discriminate between the malignant and benign outcomes selected.

Results: 26 pathology-confirmed NSCLC, 2 SCLC. 1 carcinoma whereas 12 had a benign outcome based on pathology (9) or stable follow-up CT (3). BSP data for LC cases: 26 true positives, 3 false negatives (including the carcinoma), 90% sensitivity. For benign cases, the BSP resulted in 1 false positive, 11 true negatives, 92% specificity. The overall ROC from BSP analysis was 91%.

Conclusion: BSP bioconductance measurements is associated strongly with a thoracic cancer or benignity. A technology that non-invasively provides adjunctive information to CT scanning to decide whether biopsy or further follow-up is appropriate will be an important clinical tool.

4503
Amorphous components of the extracellular matrix have impact as new biochemical markers on malignancy characterization and prognosis of non-small cell lung cancer
Maristela Peres Ranger1, Vanessa Karen de Sá2, João Roberto Maciel Martins2, Edwin Roger Parra1, Aline Mendes2, Dirce Carrasco2, Eloísa Olivieri2, Vera Luiza Capelozzi2, 1Pathology, Universidade Federal de São Paulo, São Paulo, SP, Brazil; 2Biochemistry and Molecular Biology, Universidade Federal de São Paulo, São Paulo, SP, Brazil; 3Pathology, Hospital AC Camargo, São Paulo, SP, Brazil

Introduction: Many have reported that glycosaminoglycans (GAGs) have different behaviors in the presence of malignant tissues. In this study, we examined different GAGs concentrations and their impact on diagnosis and/or prognosis of patients with non small cell lung cancer.

Methods: Sulfated GAGs and Hyaluronic Acid (HA) were examined in tumoral and non-tumoral tissues from 45 lung cancer patients. Tissue samples were dehydrated and incubated with a proteolytic enzyme. The levels of HA were measured by a noncompetitive ELISA-like fluorometric assay. The sulfated GAG chains (heparan, dermatan and chondroitin sulfate - HS, DS and CS), were precipitated, dissolved in DNAse and their concentrations were identified after gel electrophoresis.

Results: HS and HA showed significantly higher concentration in tumoral than in normal areas (p<0.02 and p<0.0001, respectively; Fig. 1A/B). The Kaplan-Meier survival curves shows that tissues with lower concentrations of HA have better long-term survival than those with higher concentrations (Log Rank=3.59; p=0.05; Fig. 1C). One hundred% of tumoral areas presented CS while the normal almost never (p=0.0001; Fig. 1D).

Conclusions: The results presented suggest a possible role of these molecules on lung cancer development, but more importantly provide potential biochemical markers for differentiating normal from lung cancer patients.

4504
Interferon (α,β, and ω) receptor 2 (IFNAR2) is a prognostic biomarker for lung cancer
Nobuhisa Ishikawa1, Noboru Hattori1, Sonosuke Tanaka1, Yasushi Horimasa1, Akihito Yokoyama1, Nobuuki Kohno1, 1Departments of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; 2Department of Hematology and Respiratory Medicine, Kochi Medical School, Kochi University, Nankoku, Japan

Background: The type I interferon receptor subunit, interferon (α,β, and ω) receptor 2 (IFNAR2), has been reported to be overexpressed in several malignancies, primarily adenocarcinomas (ADCs). However, the biological significance of IFNAR2 in human lung cancer has not yet been studied.

Methods: Immunohistochemical analysis of 113 surgically resected non-small cell lung cancer specimens was performed. Serum concentrations of IFNAR2 were also determined by an enzyme-linked immunosorbent assay in 157 lung cancer patients and 164 healthy volunteers.

Results: IFNAR2 overexpression was observed in all histological types of lung cancers examined. Furthermore, strong IFNAR2 expression was associated with shorter progression-free survival (PFS) and overall survival (OS) (p < 0.0001 and p = 0.0110, respectively) in non-small cell lung cancer patients. Multivariate analyses confirmed its independent prognostic value for PFS and OS (p < 0.0001 and p = 0.0222, respectively). IFNAR2 serum levels were also significantly higher in lung cancer patients than in healthy volunteers (p < 0.0001).

Conclusions: IFNAR2 overexpression was observed in various histological types of lung cancers, and appears to be associated with lung cancers that behave aggressively. The results of this study strongly support the potential of IFNAR2 as a diagnostic and prognostic biomarker for lung cancer.

4505
SHOX2 DNA methylation is a promising biomarker for the diagnosis of lung cancer in plasma
Bernd Schmidt1, Christoph Kneip2, Anke Seegerbarth3, Michael Fleischhacker4, Volker Liebsberg3, Dimo Dietrich3, 1Pneumology, University Hospital Halle, Halle, Germany; 2Molecular Diagnostics, Theracons GmbH, Mainz, Germany; 3Molecular Diagnostics, Bavarian Nordic GmbH, Berlin, Germany; 4Hematology · Oncology, University Hospital Charité, Berlin, Germany; 5Molecular Diagnostics, Epigenomics AG, Berlin, Germany

Background & objectives: SHOX2 DNA methylation (5mSHOX2) has been shown...
previously to identify lung cancer in bronchial aspirates and a test for 5SHOX2 is available in Europe as an IVD test to aid pathologists in the diagnosis of lung cancer. DNA methylation biomarkers can also be used to detect tumour-derived circulating DNA in blood. The objective of the present study was to develop a modified assay for detection of 5SHOX2 in plasma and to evaluate the clinical performance in patients.

Methods: A real time PCR duplex assay originally developed for quantification of 5SHOX2 in a high background of unmethylated DNA in bronchial aspirates was modified for the unique requirements of plasma. Following assay optimization, quantitative real-time PCR was used to analyze 5SHOX2 in plasma samples (n = 411). A training study was performed to determine a cut-off for patient classification (n = 20 lung cancer patients, n = 20 controls) and the resulting cut-off was verified in a testing study (n = 202 stages I – IV lung cancer patients, n = 169 controls, including patients with other cancers like e.g. of prostate).

Results: The assay reliably detected 15 pg of methylated DNA in a background of 50,000 pg unmethylated DNA. The 5SHOX2 assay differentiated lung cancer patients from controls with a specificity of 60% and a specificity of 99%. Patients with stages II (72%), III (55%) and IV (83%) lung cancer were detected at a higher sensitivity as compared with stage I patients (27%). Small-cell lung cancer (80%) and squamous cell carcinoma (63%) were detected at higher sensitivity than adenocarcinoma (39%).

Conclusions: 5SHOX2 is a promising biomarker for detection of malignant lung disease in plasma.

4506
Circulating tumor cells in chronic obstructive pulmonary disease patients
Céline Sanfienzo1,2, Karine Risso1, Vérylde Sellam1, Véronique Hofman1,3, Marius Ilie4, Elodie Long5, Eric Selva5, Christelle Bonnetaud5, Charles-Hugo Marquette1,2, Paul Hofman4,5,6,7,8,9, 10.

Introduction and hypothesis: Migration of circulating tumor cells (CTC) in the blood stream is an early event occurring during lung carcinogenesis. Chronic obstructive pulmonary disease (COPD), even in early stages, is associated with a higher incidence of lung cancer in smokers and ex-smokers. The purpose of this study was to look for the presence of CTC in a cohort of smokers having a COPD.

Methods: The presence of CTC was searched in 50 COPD patients, using both the CellSearch (CS) and the isolation by size of epithelial tumor (ISET) methods. Results: The detection of CTC in a group of 30 patients with stage IIIb or IV non small-cell lung cancer (NSCLC) and in a group of 30 healthy individuals.

Results: 80 (80%) COPD patients had CTC (mean=4; range: 2-8 CTC) detected by CS and ISET methods. 18/30 (60%) of advanced stages NSCLC patients showed CTC (mean=16; range: 2-8). 50 No CTC were detected in healthy individuals.

Conclusion: The detection of CTC using the CS and the ISET methods is a rare biological event in COPD smoker patients. In this regard, the potentiality of the CS and the ISET methods as tools for detecting early biomarkers of lung carcinogenesis is challenging.

4507
A step towards easier diagnosis of lung cancer: Detection of volatile organic compounds in air releasing tumour samples with ion- and differential mobility spectrometry
Julia Isabella Karth1, Kai Darwich1, Dirk Theagarten1, Jorg-Ingo Baumback2, Roman Parkhart1, Lutz Freitag1, 1Pneumology, Ruhrlandklinik, University Hospital Essen, Essen, Germany; 2Microfluidics and Clinical Diagnostics, RIST Europe, Saarbruecken, Germany; 3Clinical Research, Becherconsult, Bernau, Germany

Introduction: Lung cancer is the tumour with the highest mortality rate in the western world.

Unfortunately, the diagnostic process is still extensive. The detection of Volatile Organic Compounds (VOCs) in air releasing tumour samples might be a method to accelerate the process of gaining first results.

Objectives: The goal in this study was to develop a method using VOCs in the detection of characteristic peaks to determine tumour containing tissue and to specify tumour entities with air samples.

Methods: Employing an Ion Mobility Spectrometer (IMS) and a Differential Mobility Spectrometer (DMS), 30 tumour and lung samples were placed into an aluminium lung simulator and analysed by the IMS and IMS via side-stream Teflon tube. Tumour containing samples were compared to non-tumour samples from the same individual in order to distinguish between characteristic peaks. Furthermore the peaks were statistically analysed.

Results: The results showed various characteristic peaks and clusters in both measuring devices. These were able to differentiate between tumour and non-tumour samples (e.g. peak "P38", p<0,0003 in adenocarcinoma samples), as well as between the tumour entities. In addition certain peaks (e.g. "P38" in the squamous cell carcinoma samples) were lower in the tumour group.

Conclusion: VOCs are able to discriminate between tumour entities and also to detect tumour containing tissue. In future research projects IMS and DMS should be compared with a closer view on standardizing peaks in order to gain further opportunities for more precise tumour detection.

462. Appropriate use of antibiotics in respiratory infections in Europe (the GRACE project)
Sibyl Anthierens1,2,3, Sarah Tonkin-Crine1, Elaine Douglass4, Lucy Yardley4, Herman Goossens5,6, Theo Verheij7, Samoen Coenen1,2,3, 1Centre of General Practice, University of Antwerp, Antwerp, Belgium; 2Vaccine & Infectious Disease Institute (Vaxinfectios), University of Antwerp, Antwerp, Belgium; 3Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium; 4Health Psychology, University of Southampton, Southampton, United Kingdom; 5Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, Netherlands

Background: In the last stage of the GRACE project a pragmatic trial was done to assess the effects of communication training and the use of a CRP test on antibiotic treatment of lower respiratory tract infections. The current study assessed the feasibility, acceptability and acceptability of the intervention in this trial across 5 European countries (Belgium, Netherlands, Poland, Spain, UK). The aim was to elicit GP and patient attitudes before the intervention, in order to adapt the interventions as necessary.

Method: 30 GPs and 13 patients from the 5 countries were interviewed before the intervention using a "think aloud" approach. Data were coded following techniques taken from framework analysis.

Findings: GPs across all countries were supportive of the aims of the intervention, provided the strong evidence base supporting the training and found the web-based format appealing. Country-specific differences often reflected differences in health systems, and highlighted where the intervention could be tailored. The patient data highlighted the importance of the When and How of using the booklet as very important in the success of the use of the booklet. Analyses of patient data gathered during the intervention will also be presented if available.

Discussion: The findings provide valuable insights informing future development of behavioural interventions across Europe regarding antibiotic use.

4509
The effect of amoxicillin in lower respiratory tract infection (LRTI): A placebo controlled RCT in 16 primary care GRACE networks from 12 countries in Europe
Paul Little1, Beth Stuart1, Theo Verheij2, Chris Butler4, Michael Moore1, Samoen Coenen1,3, Maciek Godzycki-Cwikło6, Artur Mierzecki7, Slawomir Shlabicz8, Antoni Torres9, Jordi Almirall10, Peter Edwards11, Tom Schaberg12, Sigvard Möstl13, Francesco Biasi13, 1Centre of General Practice, University of Antwerp, Antwerp, Belgium; 2Vaccine & Infectious Disease Institute (Vaxinfectios), University of Antwerp, Antwerp, Belgium; 3Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium; 4Health Psychology, University of Southampton, Southampton, United Kingdom; 5Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, Netherlands; 6Department of General Practice, Cardiff University, Cardiff, United Kingdom; 7Department of General Practice, University of Antwerp, Antwerp, Belgium; 8Department of Family and Community Medicine, Medical University of Lodz, Lodz, Poland; 9Independent Laboratory of Family Physician Education, Pomorski Medical University, Szczecin, Poland; 10Department of Family Medicine and Community Nursing, Medical University of Białystok, Białystok, Poland; 11Serví de Pneumologia, Institut Clinic del Torax, Barcelona, Spain; 12Intensive Care Unit, Hospital de Marato, Marato, Spain; 13Ely Bridge Surgery, Ely Bridge Surgery, Cardiff, United Kingdom; 14Zentrum für Pneumologie, Diakoniekrankenhaus Rotenburg, Rotenburg, Germany; 15Unit of Research and Development in Primary Health Care, Jonkoping, Jonkoping, Sweden; 16Istituto Malattie Respiratorie, University of Milan, Milan, Italy; 17Ghent University, University Hospital, Ghent, Belgium; 18Zdravstveni dom Jesenice, Zdravstevni dom Jesenice, Jesenice, Slovenia; 19Faculty of Pharmacy, Vrije Universiteit Brussel, Brussel, Brussel, Belgium; 20University Medical Center Utrecht, Utrecht, Netherlands; 21Department of General Practice, Cardiff University, Cardiff, United Kingdom; 22Department of General Practice, University of Antwerp, Antwerp, Belgium; 23Department of Family and Community Medicine, Medical University of Lodz, Lodz, Poland; 24Independent Laboratory of Family Physician Education, Pomorski Medical University, Szczecin, Poland; 25Department of Family Medicine and Community Nursing, Medical University of Białystok, Białystok, Poland; 26Centre of General Practice, University of Antwerp, Antwerp, Belgium; 27Department of General Practice, University of Antwerp, Antwerp, Belgium; 28Department of General Practice, University of Antwerp, Antwerp, Belgium; 29Department of Family and Community Medicine, Medical University of Lodz, Lodz, Poland; 30Independent Laboratory of Family Physician Education, Pomorski Medical University, Szczecin, Poland; 31Department of Family Medicine and Community Nursing, Medical University of Białystok, Białystok, Poland; 32Centre of General Practice, University of Antwerp, Antwerp, Belgium

Introduction: LRTI is the commonest acute presentation managed in primary care and still a major driver of antibiotic prescribing. Systematic reviews of placebo controlled studies are small (<1000).

Aim: To determine the effectiveness of amoxicillin for lower respiratory tract infection.

Methods: 2054 patients presenting with uncomplicated acute cough (<4 weeks) as the main symptom were randomised to amoxicillin 1g three times a day or placebo for 7 days. Patients completed validated symptom diaries for symptom severity (7 point scale) and duration. Notes were reviewed for repeat consultations.
Results: 593 of trial population (28%) were aged 60+, and symptom severity documented and duration were documented in 87% of patients. There was no significant difference in symptoms severity in the first 4 days after seeing the doctor (placebo mean 1.69, antibiotic 1.62; difference -0.07 [0.18 to 0.00]), and no significant difference in the proportion with moderately bad or worse symptoms at 7 days (47% vs 40% respectively, p=0.07 NNT 14). Among the subgroup of patients with no COPD, there was no evidence of antibiotic benefit. 5% more patients in the antibiotic group compared with the placebo group developed nausea, rash or diarrhoea (NNH 20).

Conclusions: Antibiotics are very unlikely to provide meaningful symptomatic benefit in LRTI for most patients, and any benefit is likely to be similar to the magnitude of harm.

4510 Undetected chronic obstructive lung disorders in patients presenting with acute cough in primary care: Results from the European GRACE study

Lidewij Broekhuizen¹, Saskia van Vught², Peter Zuithof², Chris Butler², Samuel Coenen³, Herman Goossens³, Paul Little², Theo Verheji², Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; ²Department of Primary Care & Public Health, Cardiff University School of Medicine, Cardiff, United Kingdom; ³Microbiology, University of Antwerp, Wilrijk, Belgium; ⁴Faculty of Medicine and Health and Life Sciences, University of Southampton, Southampton, United Kingdom

Introduction: Cough is among the most frequently presented complaints, and a suitable opportunity to consider the presence of underlying asthma or COPD.

Aims: To determine the prevalence of undetected chronic obstructive lung disorders in patients consulting their general practitioner (GP) with complaints of cough ≤ 28 days.

Methods: For this cross sectional diagnostic study, 2532 adult patients without known asthma or chronic obstructive pulmonary disease (COPD), attending their GP with complaints of cough ≤ 28 days, were recruited from 12 European countries. Inclusion criteria were: symptom duration at day 28 after inclusion; Asthma was defined present if there were recurrent complaints of wheezing, cough or dyspnoea, and/or bronchodilator response; COPD was defined present according to two cut off values for the (post bronchodilator) ratio of the FEV1 to the forced expiratory volume in one second (FEV1/FVC ratio): 1) below 0.7 (“fixed ratio”); 2) below the lower limit of normal (LLN) according to age, gender, height.

Results: 336 subjects had asthma (13%), and according to the used definitions of COPD 1 and 2, respectively 246 (10%) and 168 (7%) subjects had COPD. Spearman’s Correlation between GOLD and LLN was 0.71. There was discrepancy between GOLD and LLN definition for COPD in especially the elderly and the very young.

Conclusions: In patients presenting acute cough, undiagnosed asthma was more frequently detected than COPD. Different definitions for obstructive spirometry results led to large differences in the proportion of patients classified with COPD.

4511 Developing clinical definitions of LRTI for research and primary care practice in Europe: A consensus study using the GRACE Network

Giles Greene¹, Kerenza Hood², Samuel Coenen³, Theo Verheji², Paul Little², Herman Goossens³, Christopher Butler², ¹Department of Primary Care and Public Health, Cardiff University, Cardiff, United Kingdom; ²South East Wales Trials Unit (SEWTU), Department of Primary Care and Public Health, Cardiff University, Cardiff, United Kingdom; ³Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; ⁴University Medical Center Utrecht, Julius Center for Health, Sciences and Primary Care, Utrecht, Netherlands; ⁵School of Medicine, University of Southampton, Southampton, United Kingdom

Introduction: Antibiotic prescriptions for LRTI accounts for a large proportion of antibiotic consumption and many of these prescriptions do not benefit patients and contribute to the growing problem of antibiotic resistance. Addressing the primary care research agenda to improve evidence-based management requires clear definitions of clinical entities.

Aims: We aimed to generate definitions for four LRTIs: community-acquired pneumonia, acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease, and acute infective exacerbations of asthma, that apply to clinical practice and low intensity investigation research settings in European primary care.

Methods: Candidate definitions elicited from the systematic review of literature and a nominal group meeting were the put to a Delphi panel of selected experts from Europe and the US over three rounds. The definitions achieving high consensus were then tested for usability by an expert panel.

Results: 253 papers met our search criteria. The nominal group meeting generated highly ranked definitions for two LRTIs. The Delphi panel considered five candidate definitions derived from the systematic review and nominal group meeting and agreed upon definitions and open comments for the expert panel to assess the “usability” of these emerging definitions.

Conclusion: We combined empirical evidence with expert opinion for the development of a set of clinically based definitions for the five most common LRTIs presenting in general practice.

4512 Detecting pneumonia in patients with acute cough in primary: Results from the European GRACE study

Saskia van Vught¹, Lidewij Broekhuizen¹, Peter Zuithof², Pin de Jong², Greet Ieven³, Herman Goossens³, Christine Lammens⁴, Samuel Coenen³, Chris Butler², Paul Little², Theo Verheji², Julius Center for Health, Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; ²Department of Respiratory, University Medical Center Utrecht, Utrecht, Netherlands; ³Department of Medical Microbiology Vaccine & Infectious Disease Institute (VAXINFECTIO), University Hospital Antwerp, Antwerp, Belgium; ⁴Department of Primary Care and Public Health, Leiden University Medical Center, Leiden, Netherlands; ⁵Department of Primary Care and Public Health, University of Southampton, Southampton, United Kingdom

Introduction: It is still unclear what the best strategy to detect pneumonia in primary care patients should be. To quantify the diagnostic value of history, physical examination and the added value of inflammation markers in detecting pneumonia in patients presenting with acute cough in primary care.

Methods: 2820 adult patients attending their general practitioner with complaints of cough ≤28 days, were recruited from 12 European countries. Patient’s history and physical examination were recorded on the day of presentation. C-reactive protein (CRP) and pro-calcitonin (PCT) were drawn from venous blood samples and chest radiographs were taken within the next three days. Pneumonia was diagnosed by chest X-ray. With multivariable logistic regression a diagnostic model was developed for diagnosing or ruling out pneumonia.

Results: 140 patients had radiographic pneumonia (5%). Symptoms and signs with independent diagnostic value were: absence of runny nose, presence of breathlessness, diminished vesicular breathing and crackles on auscultation, tachycardia (pulse >100/min), and temperature >37.8°C. Combined these items showed an area under the ROC curve of 0.70 (95% confidence interval 0.65-0.75). A combination of the 2 strongest predictors (crackles and temperature >37.8, n=30) had a positive predictive value for pneumonia of 37%. Analysis of the added value of the added of CRP and PCT is in progress. A diagnostic model will be available in the presentation.

Conclusions: Radiographic pneumonia is uncommon in adults presenting in primary care with acute cough. Brief history and physical examination can help discriminate between those at high and low risk for pneumonia.

4513 GRACE Network of Excellence: Genetic susceptibility to lower respiratory tract infections in Europe

Anna Rautaniemi¹, Tara Mull¹, Stephen Chapman¹, Christine Lammens², Margareta Ieven³, Adrian Hall³, ¹Welcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; ²Department of Medical Microbiology, University Hospital Antwerp, Antwerp, Belgium

Introduction: Lower Respiratory Tract Infection (LRTI) is one of the leading reasons for seeking medical care in Europe. However, not everyone is equally susceptible to LRTI.

Aims and objectives: To identify host genetic factors that may play an important role in explaining this inter-individual variation in susceptibility to LRTI.

Methods: DNA was extracted from blood samples of 3000 cases and 3000 matched controls recruited within the GRACE study. Single nucleotide polymorphisms (SNPs) in 19 genes, selected based on our earlier studies on severe LRTI (invasive pneumococcal disease (IPD)), were genotyped with Sequenom’s iPLEX technology. For 5 remaining genes (SOD1, IL1B, IL10, TLR4 and IFITM3), genotyping was performed with TaqMan chemistry as a second independent validation of all genotyping.

Results: SNPs in the genes PTPN22 (Arg620Trp: p=0.037, OR 2.0) and NFKBIZ (rs6156597: p=0.022, OR 0.87; rs600718: p=0.028, OR 0.87) associated with LRTI in the initial analysis which included half of the cases and controls. PTPN22 is a lymphoid specific protein tyrosine phosphatase that regulates the immune response through T-cell signalling. NFKBIZ is one of the NF-kB inhibitors and thereby affects the transcription of pro-inflammatory genes. Genotyping of the rest of the samples is ongoing. In addition, more candidate genes possibly involved in the host immune response to viral infections will be genotyped. In the further analyses, cases will be subdivided based on the microbiological cause of their LRTI, namely between bacterial and viral infection, and further to specific pathogens.

Conclusions: Host genetic factors involved in the pathogenesis of IPD might also be important in defence against milder LRTIs. Identification of these factors may potentially lead to more individualised detection, treatment, and prevention of LRTIs.

4514 Lower respiratory tract infections in the European GRACE primary care network: Bacterial causes or do viruses also matter?

Margareta Ieven¹, Katherine Loens¹, Frank Coenjaerts¹, Christine Lammens², Anouk Vandersteen³, Theo Verheji², Paul Little², Herman Goossens³, Eric Claas⁴, Anton van Loon⁴, ¹Vaccine and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium; ²Department of Virology, University Medical Center Utrecht, Utrecht, Netherlands; ³Department of Primary Care Research, University of Southampton, Southampton, United Kingdom; ⁴Department of Medical Microbiology, Leiden University Medical Center, Leiden, Netherlands

Especially the role of the newly recognised viruses is not well known in adult
lower respiratory tract infections in the community (LRTI). We investigated the role of *S. pneumoniae* (Sp), *Haemophilus influenzae* (Hi) and viruses in LRTI in the GRACE primary care network (PCN) using culture and real-time nucleic acid amplification tests (RT-NAATs). From 10/2007-04/2010 3102 patients with LRTI were enrolled in a prospective study in 16 PCNs in 12 EU countries. Nasopharyngeal swabs (NPS) and sputa for culture of *Sp* and *Hi* were collected and frozen until transport to the central lab for nucleic acid (NA) extraction. Aliquots of NA extracts were sent to the LUMC and UMC-U for detection of influenzaviruses (INF) A/B, parainfluenzavirus (PIV)-1-4, human rhinoviruses (HRV), human metapneumovirus (hMPV), respiratory syncytial virus (RSV), adenoviruses (hAdV), Bocavirus (BOCA), coronaviruses (HCoV) OC43, NL-63, 229E, polyomaviruses KI and WU by in-house RT-PCR.

In 3082/3102 patients a NPS was collected. An aetiologic agent was detected in 77% of patients: *Sp* and *Hi* in 9.1% and 14.9% respectively; a respiratory virus in 53.1%; HRV 18.6%, INF 11.1%, HCoV 7.4%, hMPV 4.4%, RSV 4.4%, polyomaviruses 2.8%, PIV 2.5%, hAdV 1.4%, BOCA 0.5%. For most viruses no significant differences were observed in prevalence between the 3 winters. In <5% of patients persistence of respiratory virus was seen in the follow up visit.

This is the largest aetiologic study on LRTI in PCNs: in ±80% of the patients a microbial agent was found; over 50% were viral infections: HRV’s account for the majority. Use of RT-NAATs results in a significant improvement of the aetiologic diagnosis LRTI.

### 463. Biomarkers in sarcoidosis

#### 4515

**The role of vitamin D3 in the local inflammatory process in sarcoidosis (SA)**

Anna Kowalska1, Elzbieta Pascinka1, Anna Golan-Geremek1, Agnieszka Skoczylas1, Justyna Czerwiawska1, Adriana Rozyl1, Paulina Jagus1, Joanna Chorostowska-Wynimko1, Dorota Górecka1, 2Laboratory of Molecular Diagnostics and Immunology, Institute of TB & Lung Diseases, Warsaw, Poland. 1Department of Respiratory Medicine, Institute of TB & Lung Diseases, Warsaw, Warsaw, Poland.

**Background**: SA is an inflammatory disease characterized by granulomas that can produce a 1,25(OH)2D hormone. No reports are available in the literature on the role of vitamin D3 derivatives in the local inflammatory process in SA.

**Aims**: To assess the role of vitamin D3 derivatives in the local inflammatory process in SA based on the determination of their concentration in the bronchoalveolar lavage fluid (BALF) as well as in exhaled breath condensate (EBC).

**Material and Methods**: In 108 pts (48 women, 60 men; mean±SD age 44.3±9.5 yrs, BMI=27.5±4.8) with SA stage I-IV we measured 1,25(OH)2D (pg/m), 25(OH)D (ng/ml) in serum and BALF as well as leukocytes, lymphocyte phenotypes CD4/CD8, alkaline phosphatase (ALP), ACE, D-dimer, fibrinogen, albumin and gammaglobulin, phosphate in serum and 24h calcium urine excretion.

**Results**: Results are shown below:

**Table 1**

<table>
<thead>
<tr>
<th>Concentration of vitamin D3</th>
<th>Mean value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>25D serum</td>
<td>15.5±8.1</td>
</tr>
<tr>
<td>1,25D serum</td>
<td>54.2±22.8</td>
</tr>
<tr>
<td>25D BALF</td>
<td>7.4±1.4</td>
</tr>
<tr>
<td>1,25D BALF</td>
<td>8.9±3.1</td>
</tr>
<tr>
<td>25D EBC</td>
<td>7.7±3.8</td>
</tr>
<tr>
<td>1,25D EBC</td>
<td>8.5±3.1</td>
</tr>
<tr>
<td>LD serum</td>
<td>4.5±3.1</td>
</tr>
</tbody>
</table>

**LD = 1,25(OH)2D/25OHD**

**Table 2**

<table>
<thead>
<tr>
<th>Correlations of vitamin D3 concentration to</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25D serum/macrophage rate in BALF</td>
<td>0.22</td>
<td>0.046</td>
</tr>
<tr>
<td>1,25D serum/lymphocyte rate in BALF</td>
<td>0.21</td>
<td>0.063</td>
</tr>
<tr>
<td>1,25D BALF/lymphocyte rate in BALF</td>
<td>0.22</td>
<td>0.043</td>
</tr>
<tr>
<td>1,25D serum/CD4/CD8 lymphocyte count in BALF</td>
<td>0.26</td>
<td>0.013</td>
</tr>
<tr>
<td>LD serum/leukocytes</td>
<td>0.34</td>
<td>0.002</td>
</tr>
<tr>
<td>LD serum/CD4 lymphocyte count in BALF</td>
<td>0.29</td>
<td>0.025</td>
</tr>
</tbody>
</table>

There was no other significant correlation between 25OHD or 1,25(OH)2D and other evaluated inflammatory markers.

**Conclusions**: Significant correlations between some inflammatory markers and 25(OH)D or 1,25(OH)2D concentration in serum may suggest a role of vitamin D3 as an indicators of inflammatory process in SA.

Supported by: Polish Ministry of Science grant No 1594/PO1/2007/32

#### 4517

**Polymorphisms in CCR5 confer susceptibility to Löfgren's syndrome and may regulate the immune response**

B. Karakaya1, C.H.M. van Moorsel1, G.T. Rijkers2, A.H.M. van der Helm3, T.W.J. Huizinga1, J.M.M. van den Bosch1, J.C. Grutters1, 1Department of Pulmonology, Center for Interstitial Lung Disease, St Antonius Hospital, Nieuwegein, Netherlands; 2Department of Medical Microbiology and Immunology, St Antonius Hospital, Nieuwegein, Netherlands; 3Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands.

**Rationale**: Löfgren’s syndrome is an acute and usually self-limiting phenotype of sarcoidosis. Several studies have found associations between specific gene polymorphisms and susceptibility to sarcoidosis. Chemokines are small peptides that mediate monocyte, lymphocyte and neutrophil chemotactic activity by binding to specific G-protein coupled receptors, such as CCR5. A study showed that the HIC haptotyope of CCR5, with single nucleotide polymorphism (SNP) rs179987, was associated with Löfgren’s syndrome.

**Objective**: We investigated if SNPs of the CCR5 gene were associated with Löfgren’s syndrome and had an effect on the B-lymphocyte response of patients.

**Methods**: Hundred and twenty patients with Löfgren’s syndrome were characterized and genotyped for 4 SNPs in CCR5. Our control cohort consisted of 313 self-reported healthy individuals.

**Results**: Carriage of the G-allele was significantly higher in patients with Löfgren’s syndrome than in healthy controls (p=0.0057, CI 1.13-2.01, OR 1.505). Twelve out of 18 patients with Löfgren’s syndrome showed no calcium response, of which 11 were carriers of the G-allele: 7 GG, 4 GA, 1 AA. Nine of these 12 patients where women. All controls showed a calcium mobilization response upon stimulation with MIP-1α.

**Conclusions**: The SNP rs179987 in the CCR5 genes is associated with Löfgren’s syndrome. Functionality assays showed that polymorphisms of the CCR5 have an impact on cellular processes that may regulate the response of B-lymphocytes.

#### 4518

**Chitotriosidase: A sensitive biomarker of sarcoidosis**

Elena Bargagli, David Bennett, Claudia Maggiorelli, Maria Grazia Pieroni, Rosa Metella Refini, Maria Grazia Perari, Paola Rottoli, Respiratory Diseases Section, Department of Clinical Medicine and Immunological Sciences, University of Siena, Siena, Italy.

Chitotriosidase is a member of family of glycosylhydrolases, enzymes involved in...
in the degradation of chitin and chitin-like substrate, identified in a wide variety of organisms. Increased concentrations of chitinidase have been reported in several lysosomal storage diseases and more recently also in sarcoidosis.

In this study chitinidase concentrations were evaluated in a population of 233 sarcoidosis patients and 70 controls in order to verify enzyme specificity and sensitivity and to evaluate chitinidase prognostic meaning. Chitinidase has been found significantly increased in serum of patients with sarcoidosis than in controls (p < 0.0001). ROC curve analysis revealed: cut-off value of 39.50 nmol/h/ml, sensitivity 89.70% and specificity 90%. The analysis of chitinidase in different phenotypic subgroups of patients revealed very high serum enzyme levels in symptomatic patients requiring systemic steroid therapy at onset and after disease relapses.

In conclusion as a new potential biomarker of sarcoidosis severity, chitinidase resulted sensitive, reproducible and easily detectable in serum.

4519 Mycobacterial heat shock protein 16 kDa, marker of dormant stage of mycobacteria, in precipitated circulating immune complexes in sarcoidosis Anna Dubaniewicz1, Adam Holownia2, Mahavir Singh4. 1Department of Pulmonology, Medical University of Gdańsk, Gdańsk, Poland; 2Department of Clinical Pharmacology, Medical University of Białystok, Białystok, Poland; 3Department of Genome Analysis, Helmholtz Center for Infection Research and LIONEX Diagnostics & Therapeutics GmbH, Braunschweig, Germany

M. tuberculosis antigens, e.g., heat shock proteins (Mtb-hsp), genetic factor and autoimmunity can act as potential causes of sarcoidosis (SA). Mtb-hsp inducing both cellular and humoral immune response may provide a link between infection and autoimmunity. We have recently demonstrated the presence of Mtb-hsp70, Mtb-hsp65 and Mtb-hsp16 in sarcoiid tissue. Higher occurrence of serum Mtb-hsp70 than Mtb-hsp65 and Mtb-hsp16 in SA patients could be caused by sequestration of Mtb-hsp65 and Mtb-hsp16 in circulating immune complexes (CIs). To test this hypothesis, we have evaluated and quantified Mtb-hsp70, Mtb-hsp65 and Mtb-hsp16 in precipitated CIs from blood of 20 patients with SA, 19 patients with active tuberculosis (TB) and 21 healthy volunteers using PEG precipitation and Western Blot. The results showed significantly increased CIs levels in SA vs TB and Control, whereas there was no difference between TB and healthy individuals. The Mtb-hsp16, Mtb-hsp65 and Mtb-hsp70 concentrations in precipitated CIs were significantly higher in SA than in TB and Control, but there was no difference between TB and Control. In all tested groups, the Mtb-hsp16 concentration was significantly increased than Mtb-hsp70 and Mtb-hsp65.

In summary, our results show increased presence of Mtb-hsp, Mtb-hsp65 and Mtb-hsp70 concentrations in healthy individuals. The Mtb-hsp16, Mtb-hsp65 and Mtb-hsp70 in precipitated CIs from blood of 20 patients with SA, 19 patients with active tuberculosis (TB) and 21 healthy volunteers using PEG precipitation and Western Blot. The results showed significantly increased CIs levels in SA vs TB and Control, whereas there was no difference between TB and healthy individuals. The Mtb-hsp16, Mtb-hsp65 and Mtb-hsp70 concentrations in precipitated CIs were significantly higher in SA than in TB and Control, but there was no difference between TB and Control. In all tested groups, the Mtb-hsp16 concentration was significantly increased than Mtb-hsp70 and Mtb-hsp65.

In summary, our results show increased presence of Mtb-hsp, Mtb-hsp65 and Mtb-hsp70 concentrations in healthy individuals. The Mtb-hsp16, Mtb-hsp65 and Mtb-hsp70 in precipitated CIs from blood of 20 patients with SA, 19 patients with active tuberculosis (TB) and 21 healthy volunteers using PEG precipitation and Western Blot. The results showed significantly increased CIs levels in SA vs TB and Control, whereas there was no difference between TB and healthy individuals. The Mtb-hsp16, Mtb-hsp65 and Mtb-hsp70 concentrations in precipitated CIs were significantly higher in SA than in TB and Control, but there was no difference between TB and Control. In all tested groups, the Mtb-hsp16 concentration was significantly increased than Mtb-hsp70 and Mtb-hsp65.

4520 Use of discriminant analysis to assess pulmonary functional worsening in patients with sarcoidosis by means of a panel of inflammatory markers Gregoriano Faustini1, Maria Kuti1, Alessandro Belli, Armanda Propati1, Angelo Sherer2, Salvatore D’Antonio3, Alfredo Sebastiani4, Giovanni Puglisi5, Giovanni Galluccio6, Sandro Batzella7. 1Department of Cardiovascular, Respiratory and Morphologic Sciences, University “La Sapienza”, Rome, Rome; 2IRC’s Fondazione Don Carlo Gnocchi – Onlus, Don Gnocchi, Milan, Italy; 3Department of Respiratory Diseases, S. Camillo-Forlanini Hospital, Rome, Italy; 4EDS Center of the Fundazione Don Carlo Gnocchi – Onlus, Don Gnocchi, Milan, Italy; 5Department of Respiratory Diseases, S. Camillo-Forlanini Hospital, Rome, Italy

Background: Sarcoidosis’ protein clinical course has prompted many studies to discover biomarkers which could help to trace disease progression and response to therapy.

Aims: In our study we performed discriminant analysis, to investigate whether a panel of selected markers measured in BALF and serum from patients with sarcoidosis would help to predict pulmonary functional worsening.

Methods: We enrolled in the study 30 consecutive individuals with sarcoidosis. At enrolment participants underwent pulmonary function tests, fiber-optic bronchoscopy and radiological evaluation. PFTs were also performed at follow-up visits during a 2 year period. Pulmonary function worsening was defined as a decline of TLC, FVC, FEV1 > 15% and DLCO > 10%. BALF differential cell counts were performed in all participants and BAL and serum ECP, MPO, Tryptase, PiHP and SiL2r concentrations were quantified by RIA and ELISA tests. Discriminant analysis was performed to optimize the accuracy of selected variables in predicting functional worsening.

Results: Pulmonary function worsening was observed in 24% of participants. Applying discriminant analysis function a high classification rate was obtained, the following formula: C= -(PMBAL x 0.18 + ECP BAL x 1.20 - MPOBAL x 0.03 + Tryptase BAL x 1.21 - PiHP BAL x 0.01 - SiL2rBAL x 0.01 -1.183), allowed the correct allocation of 100% of participants. The positive likelihood ratio was > 20 and the negative likelihood ratio was 0.

Conclusions: Our results show that a panel of BAL markers may be used to distinguish patients with stable disease from individuals with pulmonary function worsening and may help to decide therapeutic strategies.

4521 Chronic fatigue in sarcoidosis-in-clinical-remission: Psychological and physical characteristics Paper 1,2, Cobi Heijnek1, Oscar Vogel1, Jan Grutters1,4. 1Department of Pulmonology, St. Antonius Hospital, Nieuwegein, Netherlands; 2Laboratory for Neuromunomology and Developmental Origins of Disease, University Medical Center, Utrecht, Netherlands; 3Department of Neurology, St. Antonius Hospital, Nieuwegein, Netherlands; 4Division Heart & Lungs, University Medical Center, Utrecht, Netherlands

When sarcoidosis is in clinical remission, complaints of chronic fatigue often persist. The exact features of this post-infectious fatigue are unknown. This study assesses the severity of fatigue and the presence of fatigue-related symptoms in sarcoidosis-in-clinical-remission. Furthermore, we evaluate psychological distress, pain and patient-reported sleep quality, and record physical activity levels and muscle strength as objective assessments of fatigue. Lastly, we assess the severity of fatigue at a follow-up.

Methods: Seventy-five patients with sarcoidosis-in-clinical-remission were evaluated with the Checklist Individual Strength (fatigue), the SymptomChecklist-90 (psychological distress), the McGill Pain Questionnaire (pain), standardized interview (fatigue-related symptoms), sleep diary, accelerometer and muscle strength tests.

Results: Fatigue severity mean score in sarcoidosis patients in-clinical-remission was high (fatigue-severity score: 30.5±15.5), and fatigue-related symptoms were significantly more present in the fatigued patients. Median time since diagnosis was 9 years. Fatigue was significantly associated with increased psychological distress, higher pain severity scores and more pain points, reduced physical activity and reduced muscle strength. Scores on sleep quality were normal. Response at follow-up was 87%. Fatigue severity scores of the responding group were significantly higher compared to a year before.

Conclusions: Fatigue in sarcoidosis patients in clinical remission is a long-lasting and severe problem that deteriorates over time. This post-infectious chronic fatigue is associated with a constellation of psychological and physical symptoms.

464. Access to the periphery: solitary periphery nodule

4522 Usefulness of endobronchial ultrasonography with a guide sheath for diagnosing ground glass opacity lesions in sarcoidosis-in-clinical-remission: Long-term study Yasuyuki Ikawa1, Naofumi Shinagawa1, Tatsuya Takashina1, Kenichiro Ito1, Kichi Ogura1, Yuta Takeuchi1, Noriyuki Yamada1, Hajiya Ashima1, Jun Sakakibara-Komachi1, Satoshi Otsumi1, Kosuke Nakano1, Noriaki Sukoh2, Masahara Nishimura1,2. 1First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan; 2Respiratory Department, National Hospital Organzation Hokkaido Cancer Center, Sapporo, Japan

Background and purpose: It is often hard to diagnose ground glass opacity (GGO) lesions by transbronchial biopsy (TBB), because of difficulty in detecting the site of the lesions under X-ray fluoroscopy. We have reported the usefulness of TBB using endobronchial ultrasonography with a guide sheath (EBUS-GS) for small peripheral pulmonary lesions (PPLs). EBUS-GS has an advantage to detect the site of the lesions under X-ray fluoroscopy. We have reported the usefulness of GGO lesions by EBUS-GS and examined of lesions which might influence the diagnostical yield.

Methods: We retrospectively analyzed the diagnostic yield of GGO lesions by EBUS-GS and examined of lesions which might influence the diagnostical yield.

Results: Of the 67 lesions (11 pure GGO lesions and 56 mixed GGO lesions, which consist of GGO components more than 50%), 43 (64%) were not visible by conventional X-ray fluoroscopy. Thirty-eight lesions were diagnosed by TBB with negative CT sign. (31% vs. 66%; P < 0.01) ROC curve analysis revealed: cut-off of 0.81, predictability 87%, sensitivity 84%, specificity 80%, PPV 96%, NPV 74%. Decreased physical activity and reduced muscle strength. Scores on sleep quality were normal. Response at follow-up was 87%. Fatigue severity scores of the responding group were significantly higher compared to a year before.

Conclusions: EBUS-GS is a useful method for diagnosing GGO lesions. However, failure of diagnosis is associated with the lesions in smaller size and/or with negative CT sign.

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**4523**

Endobronchial ultrasound-guided transbronchial biopsy with thin bronchoscopy for peripheral pulmonary lesions

Masahide Oki, Hideo Saka, Chieyo Kitagawa, Yoshitoyo Kogure, Shigehisa Kajikawa, Naohiko Murata, Takashi Adachi, Saori Oka, Rie Tsuibo.

Department of Respiratory Medicine, Nagoya Medical Center, Nagoya, Japan

**Introduction:** Endobronchial ultrasound-guided transbronchial biopsy (EBUS-TBB) using a conventional bronchoscope has the limitation of poor bronchoscopic selection of lesions because of its large size.

**Aims and objectives:** The purpose of this study was to evaluate the diagnostic utility of EBUS-TBB using a thin bronchoscope for peripheral pulmonary lesions.

**Methods:** Data prospectively collected from 188 patients with suspected peripheral lesions who underwent EBUS-TBB using a 3.4-mm thin bronchoscope with a 1.7-mm channel and a 1.4-mm radial ultrasonic probe under fluoroscopic guidance were retrospectively analyzed.

**Results:** Thirteen patients with endobronchial lesions within the segmental bronchi that were defined as central lesions and 6 patients who did not return to follow-up were excluded from this analysis. Thus, a total of 169 patients (113 men and 56 women, median age, 67 years) with peripheral pulmonary lesions (median size, 28 mm; range, 8 to 70 mm) were included in the final analysis. The mean bronchus level reached with the thin bronchoscope was 4.6 generations. The lesion was localized with EBUS in 151 patients (91%). Diagnostic histologic specimens were obtained in 115 of 169 patients (68%; 48% [81% for lesions >30 mm, 50% for lesions >20 to <30 mm, and 17% for lesions ≤20 mm] for benign lesions and 76% [85% for lesions >30 mm, 70% for lesions >20 to <30 mm, and 65% for lesions <20 mm] for malignant lesions). Five complications (3%) occurred: 1 pneumothoraces, 1 pneumonia, and 1 moderate bleeding.

**Conclusion:** EBUS-TBB using a thin bronchoscope is an accurate method for the diagnosis of peripheral pulmonary lesions, especially malignant lesions.

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**4524**

Efficacy of endobronchial ultrasonography (EBUS) using a guide sheath (EBUS-GS) for transbronchial sampling of peripheral lung lesions

R. Mustafa, S. Abdellatif, M. Munavvar. Respiratory Medicine, Lancaster Teaching Hospitals, Royal Preston Hospital, Preston, Lancashire, United Kingdom

**Background:** Endobronchial ultrasonography with a radial scanning miniature probe provides cross-sectional images of peripheral pulmonary lesions. Ultrasonic probe covered with a guide sheath is introduced via the bronchoscope and is withdrawn after localisation of the peripheral lesion. The guide sheath is left in situ to direct sampling.

**Aims:** To assess the diagnostic yield and safety profile of this novel technique.

**Methods:** Ten patients with peripheral lung lesions were selected for EBUS-GS sampling between January 2010 and June 2010. Guided sampling was later deferred in two cases with visible endobronchial disease at conventional bronchoscopy. EBUS-GS Transbronchial biopsy (TBB) and Bronchial brush (BB) specimens were obtained. With the knowledge of subsegment leading to the peripheral lesion, additional blind TBB and bronchialveolar lavage (BAL) specimens were also acquired following removal of the GS.

**Results:** Mean size of the lesions sampled was 34 mm (22 to 52 mm). EBUS-GS TBB and BB specimens yielded a definitive diagnosis of lung cancer in five (62.5%) patients. Three patients had no malignant cells in either EBUS-GS TBB or BB specimens. In one of these three patients, malignant cells were isolated from Blind TBB and BAL specimens which had been taken in addition to EBUS-GS samples. Hence, a definitive diagnosis of cancer was obtained in six (75%) patients. The procedure was well tolerated and none of the patients suffered major bleeding or pneumothorax.

**Conclusion:** Diagnostic yield of transbronchial sampling of peripheral lung lesions is significantly improved with the use of EBUS-GS without an increase in complication rate.

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**4525**

Ultrasound guided transbronchial cryobiopsy in the diagnosis of peripheral lung lesions: A feasibility and safety trial

Ralf Eberhardt1, Mareen Schuhmann1, Korkut Bostanci2, Nicolas Kahn1, Philipp A. Schnabl1, Felix J.F. Herth1,2

1Pneumology and Respiratory Care Medicine, Thoraxklinik at the University of Heidelberg, Heidelberg, Germany; 2Department of Thoracic Surgery, Mannheim University, Mannheim, Germany

**Background:** Peripheral lung lesions (PLL) can pose a diagnostic problem since they are often difficult to reach and only insufficient material can be obtained by transbronchial forceps biopsy. Endobronchial Ultrasound (EBUS) can be used for detection and in combination with a flexible cryoprobe (Erbe Medizintechnik, Germany) larger tissue samples can be taken. The purpose of this study was to evaluate the safety and feasibility of this technique.

**Methods:** Patients with PLL up to 4 cm in diameter were enrolled prospectively. After the PLL had been identified by EBUS we performed forceps as well as cryo biopsies under fluoroscopy through a guide-sheath. The order of the techniques was randomised. The pathologist was blinded towards the biopsy technique. We evaluated and compared the diagnostic yield and sample size as well as the complication rate.

**Results:** We were able to reach the lesion with EBUS guidance in 31 of 39 patients. The final diagnosis of the 31 patients was malignant in 25 and benign in 6 cases. In 7 cases we were able to make a definitive diagnosis with bronchoscopic sampling (23%) and in 3 patients only through cryobiopsy. Samples obtained by cryobiopsy were significantly larger. Complications observed during the procedure were 1 moderate bleed after cryobiopsy treated endoscopically. No pneumothorax occurred.

**Discussion:** Transbronchial cryobiopsy with EBUS guidance is a safe technique and useful to obtain histological samples for diagnostic purposes. By obtaining larger tissue samples it may be possible to improve the bronchoscopic diagnostic yield for peripheral lung lesions.

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**4526**

Safety and tolerance of transbronchial lung biopsy with cryoprobes vs conventional forceps

Laia Garcia-Bellmunt1, Virginia Pajares1, Alfonso Torrego1, Mª Carmen Pazo1, Mª Angeles Gil2, Vicente Plaza1,1Pneumology, 2Anaesthology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

**Background:** Bronchoscopic transbronchial biopsy (TBLB) by the use of cryoprobes has been described as a feasible procedure to obtain lung samples.

**Objectives:** To determine safety of TBLB with cryoprobes vs conventional forceps. To compare the procedure length and patients’ tolerance with both techniques.

**Patients and methods:** Patients with interstitial lung diseases referred to perform a TBLB were prospectively randomized in: Group 1: cryoprobe (Erbocryo CA®) and Group 2: conventional forceps.

**Results:** Patients in group 1, under deep sedation, were intubated to allow quick cryoprobe and bronchoscope introduction and removal. Bronchoscopies in group 2 were performed under conscious sedation. Tolerance questionnaires, number of biopsies, procedure’s duration and related complications were registered.

**Results:**

- Safety and tolerance of transbronchial lung biopsy with cryoprobes vs conventional forceps

- Complication rate.

- Tolerance: Qualitative scale (a) 95.4 ± 2.0; (b) 47.8 ± 9.3 NSP

- Tolerance: Quantitative scale (cm) (b) 2.5 ± 2.2; 1.4 ± 0.8 p < 0.05

- Data is expressed as mean ± SD.

**4527**

Bronchoscopy of peripheral lung lesions: Cost-effectiveness analysis of different combinations of sampling techniques

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**Background:** Few studies have measured both the costs and the effectiveness of different combinations of sampling techniques when bronchoscopies of peripheral lung lesions are evaluated.

**Objective:** To find the most cost effective combination of sampling techniques for peripheral lung lesions not visible by bronchoscopy.

**Methods:** 289 patients were included in an open prospective trial performed at the Haukeland University Hospital and Aalesund Hospital in Norway, from June 2005 to January 2008. All sampling techniques (biopsy, brushing, trans-bronchial needle aspiration (TBNA), and washing) were performed in 178 cases (study sample). The costs from the Department of Thoracic Medicine and the Department of Pathology were calculated for each sampling technique. The combined diagnostic yield for benign and malignant disease was the effectiveness measurement. The willingness to pay for one additional positive sample was estimated to be 2800 euro, based on the cost for 5 days in a day ward and the cost of one additional investigation.

**Results:** The combination was cost-effective when the incremental cost-effectiveness ratio (ICER) was below the willingness to pay. The ICER was 1211 euro for biopsy and brushing.

**Discussion:**
compared to biopsy alone. Addition of washing or TBNA to biopsy and brushing was not cost-effective for peripheral lesions (ICER washing: 822 euro, ICER TBNA: 826 euro).

Conclusion: Biopsy and brushing was the most cost-effective combination of sampling techniques for peripheral lesions.

4528 The effect of forceps type on results and complications of transbronchial lung biopsy
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Background: Lung biopsy via the bronchoscope (TBLB) is among the routine diagnostic procedures for pulmonary diseases and is performed using either of two different kinds of forceps: cup and alligator.

Objective: The purpose of this study was to compare the efficacy of two kinds of forceps on quality of biopsy as well as the side effects of TBLB.

Methods: This was a prospective, observational and double-blind study in which four samples were biopsied from each patient via TBLB. The sample characteristics were recorded based on size, number of alveoli included, diagnostic value, and the side effects such as pneumothorax and bleeding.

Findings: A total number of 44 patients and 176 biopsies were evaluated. Twenty one patients (47.7%) were males and 23 (52.3%) females. While considering the size of samples, of 88 biopsies via alligator forceps, 21.6% were small, 45.5% medium, and 33.5% large. Corresponding results for the cup forceps were 43.2% small, 29.5% medium, and 27.5% large. From 88 biopsies taken using alligator forceps, 18.2% were found to have diagnostic value whereas in the case of cup forceps the diagnostic value was 23.9%. While no significant pneumothorax was seen with alligator forceps it was observed in 9% of the cup forceps procedures. Significant bleeding was seen in 1% of the alligator forceps and 5.7% of the cup forceps procedures.

Conclusion: Comparing two types of forceps regarding the effect on results of TBLB, alligator forceps produced larger samples (P=0.008) and less side effects (P=0.002). There was no significant difference in diagnostic value between two procedures (P=0.355).

466. COPD mechanisms

P4533 Fibrotic component in patients with emphysema reduces both exercise capacity and quality of life and increases exacerbations
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Background: Characteristics of the combined pulmonary fibrosis and emphysema (CPFE) remain to be elucidated. Little is known regarding the effect of the fibrotic component on exercise capacity, quality of life (QoL), and exacerbations.

Methods: A total of 220 smokers (current or ex-smokers) with and without COPD were recruited. The fibrotic component, defined as reticular opacities and honeycombing, was graded according to the Kazerooni score and the existence and severity of the the extent of emphysema were determined also by HRCT.

Data on age, gender, smoking history, pulmonary function, body mass index (BMI), exercise tolerance (6-min walking test; 6MWT), modified Medical Research Council (MMRC) Dyspnea Scale and Oxygen Cost Diagram (OCD); QOL, St. George’s Respiratory Questionnaire; SGRQ; and outcome data were collected. The association between the fibrotic component and exercise tolerance, QoL, and exacerbations were studied with adjustment by emphysema.

Results: The subjects (age, 68.9±9.6 years; M: 196/23) included 176 patients with emphysema and 64 patients with COPFE. The fibrotic component worsened hypoxemia during the 6MWT (p < 0.05). In CPFE, the severe fibrotic component resulted in worsened dyspnea (MMRC Dyspnea Scale, p < 0.03; OCD, p < 0.02), reduction in the distance in 6MWT with borderline significance (p = 0.08), and reduction in the minimum blood-oxygen saturation level (p < 0.01); further, the severity of the fibrotic component was positively associated with exacerbations (p < 0.04) and hospitalization (p < 0.01).

Conclusions: In CPFE, fibrotic change worsened both dyspnea and exercise capacity and also increased exacerbations.

P4534 Relationship of systemic inflammation and autoimmunity to clinically relevant outcomes in COPD
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Introduction: Chronic obstructive pulmonary disease (COPD) is associated with low-grade systemic inflammation and autoimmunity. Their relationship with relevant clinical outcomes is unclear.

Objectives: To evaluate the relationship of systemic inflammation and markers of autoimmunity with two clinically relevant outcomes, namely number of hospital admissions for respiratory disease and exacerbations.

Method: We studied 342 patients with clinically stable COPD recruited into the PAC-COPD study (68±9 yrs., FEVI 52±16% ref, FEVI/FVC 54±12%, x<SD) who were followed up for 3 years. At recruitment, we determined the serum concentration of C-reactive protein (CRP [mepholometry]), pro-inflammatory cytokines (IL6, ILB and TNFα), ELISA), oxidative stress markers (carbohydrates, nitrotyrosines, malondialdehyde (MDA) by ELISA) and circulating antimicrobial antibodies (ANA) and anti-tissue (AT) antibodies (by immunohemagglutination).

Results: We observed that, at recruitment: (1) levels of CRP (9.9±20.6 vs. 7.2±15.5 pg/ml) and IL-8 (5.6±3.9 vs. 4.8±3.4 pg/ml) were higher (p<0.01), and those of MDA lower (8.2±5.52 vs. 9.7±8.53 mM), in patients who subsequently required hospital admissions during follow up; and, (2) levels of CRP (10.8±18.6 vs. 7.8±17.5 pg/ml), carbohydrates (0.23±0.1 vs. 0.19±0.09 mmol/ml), nitrotyrosines (8.3±4.83 vs. 6.5±4.79 pg/ml) and AT antibodies (22% vs 12%) were higher (p<0.05) in patients who died during follow-up.

Conclusions: Systemic inflammation and autoimmunity influence important clinical outcomes in COPD.

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P4535 Metabolic phenotype and adipose tissue inflammation in patients with chronic obstructive pulmonary disease
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Rationale: Potential links between metabolic derangements and adipose tissue inflammation in patients with chronic obstructive pulmonary disease (COPD) are unexplored. We investigated adipose tissue tissue expression of interleukin (IL-6), tumor necrosis factor (TNF)-alpha, CD68 (macrophage cell surface receptor), caspase-3 and Bax, and their relationships to the metabolic phenotype in nine cachectic, 12 normal-weight, 12 overweight, and 11 obese patients with stable COPD (age 62.3±7.2 years).

Method: Body composition was assessed by DEXA manufacturers. Subcutaneous and visceral fat were analyzed using real-time PCR. Results: With increasing body mass index, increases in adipose tissue expressions of inflammatory or proapoptotic markers in cachectic, 12 obese patients who sub-

Conclusions: Our results suggest that adipose tissue inflammation in obese COPD patients relates to insulin resistance. Cachectic patients remained insulin sensitive, with no significant upregulation of inflammatory or proapoptotic markers in the adipose tissue.


P4536 Anemia predicts mortality after COPD exacerbation
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Anemia is a recognized prognostic factor in many chronic illnesses, but there is limited information about its outcomes in patients hospitalized due to an acute COPD exacerbation (AE-COPD).
Aim: To investigate whether anemia exert an effect on mortality after 1 year of follow-up.

Methods: From November 2007 to November 2009 we recruited 117 patients who required hospitalisation due to an AECOPD. We collected demographic data, nutritional status, hemoglobin (Hb), hematocrite (Ht) and lung function. Patients were followed up during 1 year. Mortality and days-to-death were collected.

Results: Mean age 72 (SD:4.9); FEV1, 38 (SD:12); mortality after 1 year was 21.4%. Comparing those who died to those who survived we found significant differences (p<0.000) in Hb (12.4 vs 13.8 mg/dl) and Ht (38 vs 41%). Anemia (Hb<13 g dL) prevalence was 34%. Those who died had had 4 exacerbations in previous year vs 2 exacerbations in the case of the survivors (p=0.007). Lung function and nutritional status were similar, except for muscular mass (35 vs 39%; p=0.015) and albumine (33 vs 37mg/dl; p=0.039). These variables were included in a multivariable analysis, Hb and previous exacerbations resulted as independent factors for mortality. Mortality risk for patients with anemia was 5.6 (CI: 1.6-20.1), for patients with >1 exacerbation in the previous year was 6 (CI: 1.3-127.1).

Conclusion: Anemia and previous exacerbations were independent predictors of mortality after 1 year in patients hospitalized due to AECOPD.

P4537
Relation of cardiac enzymes and echocardiographical findings with long-term mortality after chronic obstructive pulmonary disease exacerbation
Ekrem Cengiz Seyhan, Nurdan Veske, Gulsah Guinoglu, Sinem Sokucu, Mustafa Deger, Sedat Altin.

Background: Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular disease, exacerbations of which increase strain on the heart. In our study, effects of cardiac enzymes and echocardiographical findings to the long term mortality in patients with respiratory insufficiency due to COPD were investigated.

Methods: From the Yedikule hospital database, 208 patients discharged after an AECOPD attack were enrolled. Measurements of cardiac-specific enzymes (troponin, heart type fatty acid binding protein (H-FABP), NT-ProBNP, CK-MB) were available. Also echocardiography was performed.

Results: Twenty-one patients without, and 18 with severe exacerbations were enrolled (35 men; age 62.2±7.3 years). Compared to patients without exacerbation, those with the disease had lower serum levels and AT expressions of lepion, and increased serum β-crosslaps (p=0.028, p=0.034, resp.). Log AT leptin was inversely related to serum β-crosslaps (p=0.015), and directly to leptin (p<0.001) and the total, femoral, and lumbar BMD and T-score (p<0.02 for all). AT OP expression was related to all variables of bone density except for lumbar BMD (p<0.05 for all). Log AT leptin and OP expressions predicted femoral T-score indepen- dently of age, gender and pulmonary function (p<0.001, R²=0.383; p=0.008, R²=0.301, resp). Introducing body or fat mass index into these models eliminated independent predictive value of leptin and OP expressions.

Conclusion: Our results suggest that adipose tissue leptin and OP expressions are related to exacerbations in patients with COPD, and appear to act as mediators between fat mass and BMD.

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P4539
Reduced grip strength is related to frequency of exacerbations and lower health status in COPD
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Muscle weakness is a feature of COPD that affects quality of life. Systemic inflammation, an accompaniment of acute exacerbations, has been implicated in its aetiology. Recurrent exacerbations are also associated with lowered health status. This study examines the relationship between muscle weakness, health status and exacerbation frequency in a cohort of patients with COPD.

This is an observational study of 188 (95 female) COPD patients attending two hospital clinics in the North –East of England. We recorded spirometry, health status (SGRQ), grip strength (Jamar), MRC dyspnoea score and the reported frequency of exacerbations in the previous year.

Patients were aged 72.5±8.3 years with MRC score of 3±6.0±8 FEV1 of 49.2±21.5 percent predicted and a total SGRQ score of 72.2±15.5. Grip strength, expressed as a percent predicted, was 72.0±18.2 in men and 81.0±18.2 in women (mean ± SD). Exacerbations ranged from zero to five in the previous year and there were associations of reduced grip strength with exacerbation frequency (p= 0.0019) and lower health status (χ2 = 34.0; p < 0.0001).

Outcomes and number of exacerbations

<table>
<thead>
<tr>
<th>Number of exacerbations &amp; subjects</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.8±9.1</td>
<td>69.7±9.6</td>
<td>75.6±6.3</td>
<td>73.2±8.6</td>
<td>75.7±5.7</td>
<td>70.8±10.4</td>
</tr>
<tr>
<td>Male f female</td>
<td>12/11</td>
<td>3.15</td>
<td>6/7</td>
<td>24/13</td>
<td>37/53</td>
<td>11/6</td>
</tr>
<tr>
<td>% Predicted grip</td>
<td>89.62±12.9</td>
<td>91.0±12.8</td>
<td>83.2±11.6</td>
<td>70.3±10.2</td>
<td>79.9±17.9</td>
<td>48.2±10.3</td>
</tr>
<tr>
<td>SGRQ</td>
<td>53.0±15.1</td>
<td>63.3±15.1</td>
<td>68.1±15.7</td>
<td>72.5±14.3</td>
<td>79.9±17.9</td>
<td>84.6±9.9</td>
</tr>
<tr>
<td>MRC Dyspnoea Score (~1–5)</td>
<td>3.1±0.58</td>
<td>3.2±0.54</td>
<td>3.7±1.1</td>
<td>3.9±0.83</td>
<td>3.6±0.94</td>
<td>3.5±0.68</td>
</tr>
</tbody>
</table>

Conclusion: Our data clearly demonstrate that reduction in grip strength is greater in patients with a history of frequent exacerbations and is associated with reduced health status.

P4540
Gender differences in formation of endothelial dysfunction (ED) extension in COPD patients
Lyudmyla Konopkina, Tetyana Pertseva. Faculty Therapy and Endocrynology, State Medical Academy, Dnipropetrovsk, Ukraine.

ED is one of the most important branches in pathogenesis of cardio-vascularal events (CVE). It is established that soluble intercellular adhesion molecule-1 (sICAM-1) is one of the markers of ED. But it is known little about ED in COPD patients (pts) particularly in accordance with gender features.

Aim: To study the ability in prognosis of ED extension in COPD pts due to gender.

We studied 93 pts in stable phase of COPD, divided into 2 groups: 1st – 61 pts (42% of men and 58% of women); 2nd – 32 pts (35% of men and 65% of women). Measurements included clinical status, spirometry, serum level of sICAM-1 and FEV1.

Results: The level of sICAM-1 was significantly higher in male with COPD than in health male, but there were no differences between levels of sICAM-1 in female with COPD and in health female (table). Due to stages of COPD there was no correlation between sICAM-1 and FEV1 in the 1st group (p=0.175 (p<0.05)), but there was negative correlation in the 2nd group (r=-0.373 (p=0.046)).

828s
Anaemia presented with higher age (p=0.003), pH (p=0.014) and arterial oxygen known causes for anaemia were excluded.

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Background: GOLD sought to standardize COPD definition and severity. The clinical meaning of GOLD I and it progressive nature remains uncertain.

Objective: To determine the characteristics of GOLD stage I and I progression.

Methods: This research is part of the Canadian Cohort Obstructive Lung Disease (CanCOLD), a prospective longitudinal study with a population-based sample of COPD. Subjects are recruited from 9 cities in one of 4 subsets (sex and age matched): 1) GOLD GOLD ≥2, 2) GOLD I, 3) non-COPD controls, i.e., at risk (ever smoker) and healthy. Measurements were done at baseline and 3-5 years later.

Results: This preliminary analysis included 111 subjects. GOLD I subjects as compared to GOLD ≥2 had less wheezing (20% vs 41%, p=0.048), physician-diagnosed asthma (14% vs 41%, p=0.007), and better FEV1 (46% vs 46%, p=0.191) and MCS (54 vs 50, p=0.02). GOLD I subjects were less likely to have a physician-diagnosed COPD (6% vs 17%, p=0.031) and to be prescribed respiratory drugs (16% vs 30%, p=0.027). GOLD I subjects with GOLD ≥2 as compared to non-COPD control reported more dyspnea MRC ≥2 (39% vs 20%, p=0.082) but chronic bronchitis and level of health status (SF-36) were similar. Annual change in FEV1 were -62 ml/year (p=0.001) for GOLD, -32 ml/year (p=0.006) for GOLD ≥2 and 21 ml/year (p=0.001) for non-COPD. GOLD annual change in physical health (SF-36 PCS) were -0.42 (p=0.086) for GOLD, -0.89 (p=0.023) for GOLD ≥2 and -0.20 (p=0.54) for non-COPD.

Conclusion: GOLD stage I appears to be associated with more rapid decline in FEV1, and worsened health status.

Funding: CIHR Rx&D Collaborative Research Program; and the Respiratory Health Network of the FRSQ.

A366 Anemia in chronic respiratory failure

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Background: In patients with severe chronic obstructive pulmonary disease (COPD), anaemia is common and associated with impaired long-term survival and quality of life. Whether anaemia is also prevalent in patients with other severe, non-infectious respiratory diseases has not yet been systematically tested.

Methods: In 595 patients with obstructive (OD, 54.8%) or restrictive disease (RD, 45.2%) and chronic respiratory failure (CRF), anthropometric data, laboratory parameters, lung function, blood gases and co-morbidities were assessed prior to initiation of home mechanical ventilation. Patients were classified as anaemic based on haemoglobin (Hb) levels (Hb <12/13g/dl, female/male). Patients with known causes for anaemia were excluded.

Results: In patients with CRF the prevalence of anaemia was 13.5% and not different between RD (11.5%) and OD (14.7%) (p=0.276). A sex-related difference occurred only in OD (7.9% (f) versus 17.3% (m); p=0.035). Patients with OD and anaemia presented with higher age (p=0.003), pH (p=0.014) and arterial oxygen pressure (PaO2) (p=0.012), lower body mass index (BMI) (p=0.011) and total protein (p=0.012), and higher rates of coronary heart disease (p=0.011), cardiac arrhythmia (p=0.014) and diabetes mellitus (p=0.003) in comparison to non-anaemic patients. In patients with RD anaemia was associated with higher age, (p=0.008), pH (p=0.011) and lower leucocytes numbers (p=0.006).

Conclusions: Anaemia is frequent not only in COPD but also in other severe respiratory diseases combined with CRF. It was associated with advanced age, several co-morbidities, impaired nutritional state and elevations of pH and PaO2, probably due to hyperventilation. Its prognostic impact has to be elucidated in future studies.

P4543 Association of inflammation and bronchial hyperresponsiveness

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Bronchial hyperresponsiveness (BHR) is known to be linked to decline in lung function, only limited data are available as to whether BHR is associated with systemic inflammation in COPD. The present study aimed to evaluate the relationship between systemic inflammatory markers and BHR in COPD patients.

Methods: To assess serum biomarkers of patients with COPD and chronic bronchitis (CB) and to assess local and systemic inflammation in COPD depending on BHR.

Results: 111 outpatients (50-COPD II st and 9-CB) with smoking more 10 year pack/years serum concentrations IL-6, IL-8, TNF-a, CRP were analyzed. BHR was assessed in methacholine challenge. Induced sputum samples were obtained from 42 COPD patients. Results: Serum IL-6 and IL-8 in COPD patients were higher in comparison to CB patients: the medians differences were 1.44 pg/ml and 2.10 pg/ml, respectively (p<0.05). Levels TNF-a, CRP were higher in COPD patients, but did not reach statistical significance. Among CB patients BHR revealed at 1 of 9. Among COPD patients BHR revealed at 31 of 50 (62%). The pack/years were comparable in CB and COPD patients.

Conclusion: Serum IL-6 and IL-8 in COPD patients were higher in comparison to COPD patients without BHR: the means difference was 2.80 and 2.67 pg/ml, respectively (p<0.05). There were not differences between TNF-a and CRP in COPD patients depending on BHR.

COPD patients with BHR had significantly higher numbers of total cell counts and macrophages in induced sputum than COPD patients without BHR: 3.63 vs 2.30 ×10^6 cells/mL and 1.31 vs 0.37 ×10^6 cells/mL (p<0.01). No differences were found for FEV1, and Sputum eosinophils in COPD patients with BHR compared to non-BHR.

P4544 Body mass index, central obesity, and severity of chronic obstructive pulmonary disease (COPD)

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AIM: To assess impact of body mass index (BMI) and central obesity (CO) to COPD severity.

Material and methods: We performed a cross-sectional study including 248 subjects with COPD aged 40-70 yrs with smoking experience 18-25 yrs and more than 15 cigarettes smoked per day. The first group consisted of 123 obese subjects, i.e. BMI >30, while the second group included 125 subjects with CO, i.e. waist circumference >102 cm for men and 88 cm for women.

Results: In the first group we found 17 subjects with mild COPD (13.8%), 79 subjects with moderate COPD (64.2%), 25 subjects with severe COPD (20.3%), and 2 subjects with very severe COPD (1.6%). The distribution of the subjects with COPD in the second group was as follows: mild COPD 54 subjects (43.2%), moderate COPD 52 subjects (41.6%), severe COPD 14 subjects (11.2%), and very severe COPD 5 subjects (4.0%). The difference in the distribution of the subjects by COPD severity between two groups was statistically significant (P < 0.05).

Conclusions: Our results suggest that body weight and central obesity may play a role in COPD severity.

P4545 The expression of brain-derived neurotrophic factor in hippocampal and serum of chronic obstructive pulmonary disease model rats

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Objective: In clinic,we have found that cognitive impairment frequently occurs in chronic obstructive pulmonary disease (COPD) patients, but little is known about its pathogenesis. And, researchers confirmed that brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of cognitive impairment and is affected by many factors, for example, smoking, infection, hyperfusion,
Changes in arterial stiffness during COPD exacerbations
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Academic Unit of Respiratory Medicine, UCL Medical School, London, United Kingdom

Arterial stiffness is a validated measure of cardiovascular risk and is increased in COPD. Risk for cardiovascular events is higher during COPD exacerbations (Donaldson et al. Chest 2010). We hypothesised arterial stiffness would increase at exacerbation compared to the stable state.

We measured carotid-femoral aortic pulse wave velocity (APWV) using Visceromat™ apparatus in 55 patients from the London COPD Cohort in the stable state and at exacerbation onset, prior to therapy, defined by two consecutive days of new or increased symptoms requiring one major (dyspnoea, sputum purulence, sputum volume) and another major or minor symptom (coryza, wheeze, sore throat and cough). Median time from exacerbation symptom onset to APWV measurement was 4 days and a mean interval of 42 days between the paired measurements.

Demographics and Clinical Characteristics of 55 COPD Patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Stable State</th>
<th>Exacerbation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) Age (years)</td>
<td>71.8 ± 8.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male Gender</td>
<td>56%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median (IQR) Smoking (pack years)</td>
<td>47.0 (16.5-78.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean (± SD) BMI (kg/m²)</td>
<td>26.5 ± 5.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean (± SD) FEV₁ (L)</td>
<td>1.15 ± 0.41</td>
<td>1.02 ± 0.39</td>
<td>0.145</td>
</tr>
<tr>
<td>Median (IQR) FEV₁ (predicted)</td>
<td>67.6 ± 16.2</td>
<td>44.0 ± 13.3</td>
<td>0.160</td>
</tr>
<tr>
<td>Mean (± SD) FVC / FVC Ratio</td>
<td>0.47 ± 0.15</td>
<td>0.44 ± 0.13</td>
<td>0.371</td>
</tr>
<tr>
<td>Mean (± SD) SaO₂ (%)</td>
<td>94.7 ± 2.2</td>
<td>93.9 ± 2.7</td>
<td>0.135</td>
</tr>
<tr>
<td>Mean (± SD) Systolic BP (mmHg)</td>
<td>137.1 ± 20.1</td>
<td>139.7 ± 16.6</td>
<td>0.592</td>
</tr>
<tr>
<td>Mean (± SD) Diastolic BP (mmHg)</td>
<td>80.0 ± 10.9</td>
<td>81.5 ± 11.6</td>
<td>0.604</td>
</tr>
<tr>
<td>Mean (± SD) Heart Rate (beats/min)</td>
<td>76.0 ± 12.9</td>
<td>84.0 ± 13.8</td>
<td>0.029</td>
</tr>
<tr>
<td>Median (IQR) CRP (mg/L)</td>
<td>4.0 (2.0-8.5)</td>
<td>14.0 (4.0-42.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean (± SD) APWV increased by 10.4% from 9.17±1.155ms⁻¹ in the stable state to 10.12±1.85ms⁻¹ at exacerbation (p<0.001) with no significant change in blood pressure.

Arterial stiffness increases during COPD exacerbations and is a potential mechanism of increased cardiovascular risk at this time. This raises the possibility of directly targeting arterial stiffness during exacerbations of COPD.

Total serum bilirubin levels are not related to the severity of COPD
Program Development Center, Ciro, Horn, Netherlands

Introduction: It was recently reported that lower serum total bilirubin (tBLN) levels are associated with higher incidence of COPD and all-cause mortality, after adjustment for other risk factors, including smoking [1]. Aim of this study was to investigate whether serum total bilirubin levels are related to the degree of airflow limitation and other determinants of severity of COPD.

Methods: Data were extracted from the records of 1239 patients with COPD (58% males, age 64±10y, FEV₁ 46±19%, BMI 25.4±4.3kg/m²) referred for pulmonary rehabilitation. Serum tBLN ≤22μmol/L was an exclusion criterion. Lung function (FEV₁, diffusion capacity (DL CO)), arterial blood gases, body composition and six-minute walking distance (6MWD) were measured as part of integrated assessment of health status.

Results: tBLN levels were comparable in all GOLD stages. In male patients tBLN levels were 12.0±4.2μmol/L (GOLD 1), 12.1±4.0μmol/L (GOLD 2), 12.7±3.7μmol/L (GOLD 3) and 11.8±3.3μmol/L (GOLD 4), while levels were 10.8±3.7μmol/L (GOLD 1), 10.6±3.0μmol/L (GOLD 2), 10.2±3.6μmol/L (GOLD 3) and 10.6±3.8μmol/L (GOLD 4) in female patients (all p<0.001 vs males). tBLN levels were not related to FEV₁, arterial pO₂, BMI, number of pack years or 6MWD. A statistically significant but weak bivariate correlation was observed between tBLN and arterial pCO₂ (r=-0.084, p=0.01) and DL CO (r=-0.070, p<0.01).

Discussion: Serum total bilirubin levels are neither related to the degree of airflow limitation nor to other variables of disease severity in patients with COPD. Further research is needed clarify a possible contribution of low tBLN levels to the development of COPD.

Reference:

Arterial stiffness measurements in COPD: Reliability over time
Anant R.C. Patel, Alex J. Mackay, Beverly Kowlessa, Gavin C. Donaldson, Jadwiga A. Wedzicha, John R. Hurst. Academic Unit of Respiratory Medicine, UCL Medical School, London, United Kingdom

Measuring arterial stiffness is a non-invasive method of assessing cardiovascular risk and is raised in COPD. It is not known if this measure remains consistent over time in COPD, creating uncertainty in interpreting single measurements.

We measured carotid-femoral aortic pulse wave velocity (APWV) using Visceromat™ apparatus in stable patients from the London COPD Cohort (no exacerbations recorded on daily symptom diary cards in the preceding four weeks and subsequent two weeks).

APWV was measured at two visits in 89 stable patients and at a third visit in 27 of those patients. The median (IQR) interval was 103 (91,175) days between visits one and two, and 91 (84,98) days between visits two and three.

Demographics and Clinical Characteristics of 89 Stable COPD Patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mean ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.9 ± 9.1</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.97 ± 0.55</td>
</tr>
<tr>
<td>FEV₁ (Predicted)</td>
<td>52.2 ± 19.6</td>
</tr>
<tr>
<td>FEV₁ / FVC Ratio</td>
<td>0.67 ± 0.13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 5.6</td>
</tr>
</tbody>
</table>

| Percentage                   |                      |
| Male Gender                  | 63%                    |
| Current Smoking              | 20%                    |

Mean (± SD) APWV was 9.57±1.90ms⁻¹, 9.42±1.52ms⁻¹ and 9.47±1.67ms⁻¹ at
Cystic fibrosis: new basic, clinical and bacteriological knowledge

P4S50

Ciliary beat frequency in nasal and bronchial epithelial cells in patients with cystic fibrosis

Samta Alkaidic, Friedrich Horak, Thomas Frischer, Edith Nachbaur, Sabine Renner, Saskia Gruber. Department of Pediatrics, Medical University of Vienna, Vienna, Austria

Background: The extent to which altered ciliary function plays a role in the decrease in mucociliary clearance in cystic fibrosis (CF) patients is unclear.

Objective: To study ciliary beat frequency (CBF) in nasal and bronchial epithelial cells of children with CF.

Methods: Nasal and bronchial brushings were performed on 11 CF children (mean age: 8.86±4.54) undergoing bronchoscopy. In 15 healthy controls (mean age: 11.47±4.7) undergoing endoscopic procedures, nasal brushings were performed. The biopsies were performed using an Olympus BC-202D-2010 disposable brush. The samples were transported in a Medium 199 HEPES buffer and immediately analyzed. Slides were put into a climate chamber preheated to 37°C and viewed through an inverted phase contrast video microscope (Olympus IX-51). Short videos of ciliated cell groups were filmed with a high-speed video camera (Olympus Camera System) and analyzed. Slides were put into a climate chamber preheated to 37°C and viewed through an inverted phase contrast video microscope (Olympus IX-51). Short videos of ciliated cell groups were filmed with a high-speed video camera (Olympus Camera System) and analyzed.

Results: Nasal CBF in CF patients was higher when compared to that of healthy controls (mean±SD: 15.4±3.03 vs. 12.92±2.37, p<0.05). Furthermore, nasal CBF in CF patients was found to be higher than bronchial CBF (mean±SD: 13.23±2.38, p<0.05) and the values were found to correlate (r=0.7, p<0.05).

Conclusion: Our results indicate that CF patients indeed have altered nasal ciliary function. Whether these findings could have therapeutic implications requires further study.

P4S51

Molecular structure, packing and release of MUC2 with relevance to cystic fibrosis

Harriet Nilsson1, Daniel Ambert2, Gunnar Hansson1, Hans Hebert1,3,4

1Department of Bioscience and Nutrition, Karolinska Institute, Huddinge, Sweden; 2Department of Medical Biochemistry, University of Gothenburg, Gothenburg, Sweden; 3School of Technology and Health, Royal Technical High School, KTH, Huddinge, Sweden

In Cystic Fibrosis extremely viscous fluid is built up likely connected to impaired release and expansion of mucus. MUC2 is mainly expressed in small and large intestine, but also in inhaled airways, and it is stored as a multimer in secretory granules of goblet cells at high [Ca²⁺] and low pH. The extracellular milieu have to trigger the unpacking of MUC2 controlled by its N-terminus, a not yet fully understood process. The aim is to elucidate organization and structure of MUC2 when it is packed and secreted.

The N-terminal part of MUC2 was expressed in CHO cells. The secreted trimerized recombinant mucin was purified from culture medium by anion exchange chromatography. Crosslinked samples were purified by density ultracentrifugation. Analysis was performed by transmission electron microscopy (TEM). The pH in the buffers was varied in the range from 5.2 to 8 to mimic conditions of secretory pathway and extracellular environment by adding HAc (pH 5.2), MES (pH 6.2) or Tris (pH 7.4 and pH 8) with or without calcium. Samples were adsorbed onto carbon coated EM grids and negative stained. Processing of micrographs was performed using EMAN1 software.

When pH was low and or calcium present, rings with an outer and inner diameter of 25-30 and 20-25 nm respectively were observed. Without calcium rings were assembled at pH 5.2 and 6.2, but vanished with increasing pH. 2D refinements of the projections showed rotational 5- or 6- fold symmetry. Assemblies of laterally concatenated rings were obtained in the high density fraction of MUC2 N-terminus. The formations of these rings are probably vital for proper packing and release of full length MUC2. Harriet N. and Daniel A. have contributed equally.
pulmonary acceleration time (PAT) to assess pulmonary hypertension (PH) in cystic fibrosis (CF).

**Methods:** Prospective multicenter longitudinal study of CF patients with forced expiratory volume in one second (FEV1) <60% predicted evaluated during their yearly check up with echocardiography, spirometry, and nocturnal oximetry.

**Results:** Sixty-seven consecutive patients were included (mean age 17±10 years, and mean FEV1 42±12% predicted). Eight patients received a lung transplant during a mean follow-up of 19±6 months. Systolic pulmonary artery pressure (sPap) was measurable using TR peak velocity in 50 (75%) patients, with 10 having values above 35 mmHg. PAT determined in all patients correlated negatively with sPAP (r=0.36, p=0.01). Patients in the lowest PAT tertile (<101 ms) had lower FEV1 and greater nocturnal oxygen desaturation and left ventricular diastolic dysfunction and were more often on the lung transplant waiting list than patients in the other two tertiles. Kaplan-Meier curves showed a significantly shorter lung FEV1 and greater nocturnal oxygen desaturation and left ventricular diastolic dysfunction and were more often on the lung transplant waiting list than patients in the other two tertiles. Kaplan-Meier curves showed a significantly shorter lung FEV1 and greater nocturnal oxygen desaturation and left ventricular diastolic dysfunction and were more often on the lung transplant waiting list than patients in the other two tertiles.

**Conclusion:** PAT less than 101 ms is a useful prognostic indicator in patients with CF whatever the age and is determined by FEV1 and nocturnal oxygen desaturation.

**P4554**

Non invasive ventilation for advanced cystic fibrosis lung disease in children

Elaine Chan, Jay Panicker, Biju Thomas. Paediatric Respiratory Medicine, Royal Manchester Children’s Hospital, Manchester, United Kingdom

**Background:** Although non-invasive ventilation (NIV) is frequently used for respiratory failure in adult Cystic Fibrosis (CF) patients, the experience in children is limited.

**Aim:** To review the experience of using NIV for advanced CF lung disease in children at a large tertiary centre.

**Methods & Results:** Retrospective review of medical records. Setting: Royal Manchester Children’s Hospital, Manchester, U.K.

**Results:** The CF service at the Royal Manchester Children’s Hospital (Manchester, UK) looks after approximately 350 children with CF. Over a period of two years (Feb 2009-Feb 2011) 7 children (Median [range] age: 15 [11-18] years, 6 females) with advanced CF lung disease were commenced on NIV. The median [IQR] FEV1 (% predicted) was 27 [23-31]. In all children, NIV was commenced during an acute respiratory exacerbation and subsequently continued in all except one child who did not tolerate NIV. The indications for initiating NIV included one or more of the following: nocturnal and/or diurnal hypoxia, hypercapnoea, morning headaches, to aid airway clearance and to assist to the lung transplant evaluation. All children received NIV using the pressure support mode with face/nasal mask interface. Two children died whilst on transplant waiting list. Median (range) usage was 8 (2-8) hours/night. Median (range) duration of use was 6 (1-24) months. None experienced any complication related to NIV. All children on NIV achieved improved gas exchange.

**Conclusion:** Although there is growing experience of using NIV in advanced CF lung disease in children, a number of unanswered questions remain. Long term prospective multicentre studies would help develop guidelines for use of NIV in this group of patients.

**P4555**

Glucose tolerance during pulmonary exacerbations in children with cystic fibrosis

John Widger1, Mark Oliver2,ergus Ferguson3, Sarah Ranganathan3, Phil Robinison3, 1Respiratory, Royal Children’s Hospital, Melbourne, VIC, Australia; 2Gastroenterology, Royal Children’s Hospital, Melbourne, VIC, Australia; 3Endocrine, Royal Children’s Hospital, Melbourne, VIC, Australia

**Introduction:** Patients with cystic fibrosis (CF) and normal glucose tolerance (NGT) may exhibit diabetic glucose tolerance during pulmonary exacerbations [1].

**Aims:** We examined glucose tolerance during exacerbations in children with CF and compared continuous glucose monitoring (CGM) with the gold standard oral glucose tolerance test (OGTT).

**Methods:** Children with CF aged at least 10 years hospitalised with an exacerbation were recruited. Those with diabetes and those on corticosteroids were excluded. On admission, patients had an OGTT and were fitted with a CGM for 3 days. Six weeks post discharge both tests were repeated.

**Results:** Ten patients (3 males), mean age 13.9 years, have completed the study. Two patients had CCM alone, 4 patients had OGTT alone and 4 patients had both tests. By OGTT criteria, 3 were diabetic, 3 had NGT and 2 had impaired glucose tolerance (IGT) during exacerbations. Glucose tolerance status did not change between exacerbation and follow-up although mean 2-hour glucose fell from 9.7 mmol/l to 8.6 mmol/l on repeat testing (p=0.012). For CGM (n=6), mean time spent with glucose > 7.8 mmol/l fell from 7% during exacerbation to 4.3% when well (p=0.04). All 3 patients with NGT and 1 with IGT on OGTT had transient hyperglycaemia ≥11.1 mmol/l on CGM during exacerbations.

**Conclusions:** In contrast to previous published research, we found that glucose tolerance status, as determined by OGTT, remains unchanged during exacerbations. Patients with NGT and IGT had transient hyperglycaemia on CGM.

**References**

**P4556**

Pre-procedure antibiotics and effect on microbiological yield from broncho-alveolar lavage fluid in children with cystic fibrosis

Sonal Kansra1, Alan Smyth2, Carol Bertenshaw1, Amanda Ward1, Matthew Hurley2, Jayesh Bhatt3, 1Children and Young People’s Cystic Fibrosis Unit, Nottingham Children’s Hospital, Nottingham, United Kingdom; 2Academic Department of Child Health, Nottingham University, Nottingham, United Kingdom

Bronchoscopy and broncho-alveolar lavage (BAL) is widely used in children with cystic fibrosis (CF) to obtain reliable lower airway specimens for microbiological analysis. This is done under general anesthetic (GA) or sedation. GA could lead to a significant decline in pulmonary function. This is recommended that preparation for surgery should involve physiotherapy and judicious use of antibiotics to treat any evidence of infection. However if antibiotics are given pre-procedure, microbiological yield of BAL could be reduced.

**Methods:** We reviewed the records of children with CF undergoing bronchoscopy and BAL at our centre to see if there was a difference in rates of microbiological isolation if children with CF had antibiotics pre-procedure. BAL was collected in line with ERS task force 2000 recommendations.

**Results:** 36 of the 86 bronchoscopies done between 2005 and 2010 were in children with CF. BAL results from 2 children were not available. BAL showed bacterial growth in 21 (62%) of cases and atypical mycobacteria in 1 child. Children who did not have pre-procedure antibiotics were more likely to have bacterial isolates from BAL fluid as compared to children who had antibiotics pre-procedure (p=0.017) as shown in the table.

**Conclusions:** Although there may be a bias because of its retrospective nature, this study indicates that pre-procedure antibiotics in children with CF undergoing bronchoscopy for getting a gold standard microbiological sample leads to a significantly lower microbiological yield.

**P4557**

Inspiratory and expiratory respiratory reactance at 5Hz in adult cystic fibrosis

Katharine Hurt1,2, Paolo Paedri3, Harpal Kalsi2, Margaret Hodgson1, Dina Bilton1, Omar Usman1,4, Cystic Fibrosis, Royal Brompton Hospital, London, United Kingdom; 2Airway Disease Section, National Heart and Lung Institute, Imperial College, London, United Kingdom

**Introduction:** Progressive airways obstruction is a key feature of cystic fibrosis (CF) which has its origins in the small airways. Reactance at 5Hz (X5), measured by impulse oscillometry (IOS), determines the capacitative properties of the peripheral lung. In COPD patients the respiratory phase difference in X5 inspiratory minus expiratory (ΔX5) identifies individuals in ERS which is likely to benefit from NIV. Studies in CF, so far, have analysed whole breath impulse oscillometry. Aims: To determine the relationship between inspiratory and expiratory phase X5 and spirometry and body plethysmography.

**Methods:** Within-breach analysis of IOS (Jaeger) was performed on 25 patients with CF (FEV1 range 26-119% of predicted). Results were correlated with spirometric and plethysmographic indices (Jaeger MasterLab).

**Results:** Both inspiratory and expiratory X5 correlated with FEV1 (p= 0.842, p<0.0001; r=0.892, p<0.0001), respectively. The parameters showed greater sensitivity at lower FEV1 values. They also demonstrated an inverse linear relationship with RV/TLC% (r=-0.747, p<0.0001; r=-0.317, p<0.0001). Respiratory phase difference in X5 inspiratory minus expiratory (ΔX5) correlated with FeNO and RV/TLC% (p=0.562, p<0.0001; r=0.659, p<0.004). There was a greater unit change in ΔX5 in CF patients with lower FEV1 values (greater disease severity).

**Conclusion:** Measurement of inspiratory and expiratory X5 are useful indices of airway obstruction and gas trapping in CF IOS is quick, easy and portable to use at the patient bedside or outpatient clinic in contrast to body plethysmography. Calculating respiratory phase difference in X5 (ΔX5) may be a useful marker for identifying CF patients who have expiratory flow limitation.

**P4558**

Lung clearance index (LCI) at age 4-4.5 years vs lung function and chest X-ray (CXR) scores at age 7 years in children with CF

Anders Lindblad1, Fatma Aljasim1, Per Gustafsson1,2, 1Pediatrics, Gothenburg CF Centre, Queen Silvia Children’s Hospital, Gothenburg, Sweden; 2Pediatrics, Central Hospital, Skövde, Sweden

**Background:** LCI from SF6 multiple breath washout (MBW) is more sensitive than spirometry to detect early lung disease and correlates closely to CT lung changes in older subjects [1].

Aim: To see if increased LCI during the preschool period correlates to elevated pulmonary function and chest X-ray (CXR) scores at age 7 years in children with CF.

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Lung function testing is a means of monitoring progression of lung disease in cystic fibrosis (CF). Studies investigating Multiple Breath Washout (MBW) measurements in children older than 2 years with CF have shown lung clearance index (LCI) to be significantly greater in CF than in a reference population. Bronchodilators are used in CF to facilitate airway clearance and provide protection against potential bronchoconstrictors, ie, DNase, hypertonic saline and inhaled antibiotics.

**Aim:** 1. To compare LCI values among CF preschoolers, and healthy controls, 2. To compare LCI with atopy and 3). To assess the effect of the combination of inhaled steroids with long-acting beta two agonists (LABA), among CF preschoolers, by changes in LCI values.

**Method:** Twenty-eight children with CF, and recurrent cough and wheeze, aged 2 to 5 years and 27 healthy controls performed MBW measurements. Children with CF received prophylaxis with inhaled corticosteroids + LABA for 6 months. History of atopy was recorded and total serum IgE was measured. The primary endpoint was change of LCI values.

**Results:** Children with CF had significantly higher LCI compared to controls (mean difference [95% CI] 2.6 [1.8, 3.7], p<0.001). LCI values were not correlated with history of atopy (p=0.128), or total IgE (p=0.318, R=0.247). Six months after treatment with combination of inhaled steroids + LABA, LCI was reduced significantly (mean difference [95% CI] -1.19 [-3.6, -1.01], p<0.0036).

**Conclusions:** Combination of inhaled steroids + LABA seem to improve lung function among preschooler with CF, as measured by LCI.

**Discussion:** Inclusion of preschoolers was important as it is the age when children have the highest LCI. Little is known about the effect of inhaled steroids on LCI in this age group. LCI increases with age and children with CF have higher LCI compared to controls. The combination of inhaled steroids + LABA improve LCI. LCI changes correlate with age, which suggests that LCI changes are age related. This study adds new knowledge on the management of preschoolers with CF.

**References:**

**P4565**

**Combination of inhaled corticosteroids and long acting beta two agonists improve lung clearance index (LCI) in preschoolers with cystic fibrosis**

Elpis Hatzigiourou, Vasiliki Avramidou, Sophia Botkarivova, Fotis Kirvasilis, John Tsanakas. Paediatric Pulmonology Unit, 3rd Paediatric Dept, Hippokration Hospital, Aristotle University, Thessaloniki, Greece

**Background:** Lung function testing is a means of monitoring progression of lung disease in cystic fibrosis (CF). Studies investigating Multiple Breath Washout (MBW) measurements in children older than 2 years with CF have shown lung clearance index (LCI) to be significantly greater in CF than in a reference population. Bronchodilators are used in CF to facilitate airway clearance and provide protection against potential bronchoconstrictors, ie, DNase, hypertonic saline and inhaled antibiotics.

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**References:**

**P4566**

**Frequent detection of rhinovirus in bronchoalveolar lavage samples from children with cystic fibrosis**

Elisabeth Kieninger1, Caroline Tapparelli2, M.-N. Kronig1, F. Singer1, P. Latzin1, Hui-Leng Tan1, Cara Bossley3, C. Casaulta1, Andrew Bush1, Jane C. Davies1, Laurent Kaiser2, Nicolas Regamey1, 1Division of Paediatric Respiratory Medicine, University Children’s Hospital, Bern, Switzerland; 2Laboratory of Virology, Division of Infectious Diseases, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland; 3Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom

**Background:** Rhinovirus (RV)-induced chest exacerbations are common in cystic fibrosis (CF) and have been associated with impaired virus clearance by the CF airway epithelium.

**Hypothesis:** As a consequence RV can be frequently detected in lower airways of CF children.

**Patients and methods:** Bronchoalveolar lavage (BAL) samples were collected from children (n=93), non-CF bronchiectasis (n=26), asthma (n=19) and control children without lower respiratory tract disease (n=21) at a median (IQR) age of 6.7 (5.0-10.8) years. RV load was assessed by RT-PCR. Prevalence of RV infection and RV load were compared between groups and related to demographic and clinical parameters.

**Results:** RV was detected in 58 samples (36% of total) and more often in younger children (<5 years of age (29 vs. 18%). RV prevalence was highest in CF (41%) compared to non-CF bronchiectasis (23%), atopic (32%) and healthy children (6.7% (0.4-6.5%) (p=0.01). RV prevalence was similar in CF patients in whom BAL was performed during chest exacerbation (p=0.2) and phases of clinical stability (p=0.17). However, RV load was higher during exacerbation (559 [20-3380] × 10^3 vs. 25 [5.8-277]) × 10^3, (p=0.01) and inversely related to FEV1 (r=0.32, p=0.003).

**Conclusions:** RV is frequently detected in the lower airways of CF children. High RV loads during chest exacerbations and in children with advanced lung disease suggest a possible role for RV in CF lung disease progression.
**P4563**

**Title:** Cystic Fibrosis (CF) and the impact on CF disease progression are still under debate.

**Authors:**
-OBJECTIVES: To study clinical variables associated with MRSA infection and determine the impact on FEV1 evolution in CF patients.
-**Methods:**
  - A retrospective case-control study from 2002 to 2010, comparing clinical variables and decline of FEV1 of MRSA positive patients with age and sex matched controls.

**Results:**
- Thirty of the 165 CF patients (18.2%) had cultures positive for MRSA.
- Excluding patients under 4 years, the prevalence became 15.2% (23/151).
- Chronic respiratory infection was found in 19/36 (52.8%) cases reported among adolescents and adults in absence of vaccine or natural boosters.
- CF is the commonest genetically inherited disease, leading to bronchiectasis.
- Cough is a non-specific symptom in CF patients and whooping cough could cause lung function worsening.

**Conclusions:**
- The FEV1 recorded one year prior to, and at the moment of MRSA infection, was not significantly different from that obtained in controls. However, FEV1 decline over 2 and 6 years periods, were significantly greater in the MRSA group than in the controls.
- In fact, over a 6 year period FEV1 decline amounted to -2.6% versus -1.3% predicted per year in the MRSA group and controls respectively (p=0.031).
- **Conclusion:** Prevalence of MRSA in CF patients averaged 15%, and MRSA infection was shown to be associated with particular genotypic presence of bronchiectasis and hospitalization. Our spirometric data also clearly show that a MRSA episode entails an FEV1 decline that is almost double that predicted for CF patients who can remain unaffected by MRSA.

**P4564**

**Title:** Effect of recurrent growth of aspergillus on lung function in paediatric population with cystic fibrosis (CF)

**Authors:**
- **Background:** Allergic bronchopulmonary aspergillosis (ABPA) is well described in CF. Many CF patients grow Aspergillus fumigatus (AF) on sputum and cough swabs but do not have ABPA. There is evidence that this is clinically important in CF. Many CF patients grow Aspergillus fumigatus (AF) on sputum and cough swabs but do not have ABPA. There is evidence that this is clinically important in CF.

**Hypothesis:** Isolation of AF from sputum or cough swab is associated with a worse clinical state in CF children.

**Methods:** A retrospective cohort study of all children with CF who had sputum samples or cough swabs positive for AF on >1 occasion at least one month apart between 2008 and 2010. Lung function results and nutritional status were recorded.

**Results:**
- 35 children (15 male) were identified who fit the criteria, mean age 11.2 years (SD2.1) mean BMI 17.5. Data were collected on 21 controls (7 male) with CF who had not grown AF during the study period and had never had a diagnosis of ABPA, mean age 11.12 years (SD2.21) mean BMI 17.2. Children with AF had a lower mean FEV1 (p=0.0001) over the follow-up period (69.8, SD13.8 vs 89.4, SD11.5), despite a greater number of days of intravenous antibiotics (45 days vs 2.6 days in the 2 year period (p<0.0001)).

**Conclusions:**
- Recurrent growths of AF are associated with a worse clinical state, manifest by lower lung function, despite the use of significantly more intravenous antibiotics.

**P4565**

**Title:** Prevalence and reservoirs of A. xylosoxidans and S. maltophilia in cystic fibrosis center

**Authors:**
- **Background:** Allergic bronchopulmonary aspergillosis (ABPA) is well described in CF. Many CF patients grow Aspergillus fumigatus (AF) on sputum and cough swabs but do not have ABPA. There is evidence that this is clinically important in CF. Many CF patients grow Aspergillus fumigatus (AF) on sputum and cough swabs but do not have ABPA. There is evidence that this is clinically important in CF.

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**Conclusions:**
- Recurrent growths of AF are associated with a worse clinical state, manifest by lower lung function, despite the use of significantly more intravenous antibiotics.

**P4566**

**Title:** Quality of life of paediatric patients with cystic fibrosis and their caregivers

**Authors:**
- **Introduction:** Cystic fibrosis (CF) is the most common fatal genetic disease which has a significant impact on patient’s and their caregiver’s daily life.

**Objective:**
- The aim of the study was to determine the quality of life (QoL) of children with CF and their parents and to compare the impact of CF on daily life to that of asthma.

**Methods:**
- The Cystic Fibrosis Questionnaire (CFQ) was used to measure the QoL of children with CF and their caregivers. PedsQLTM 4.0 Generic Core Scale was used to determine the QoL of patients with CF.

**Quality of life of patients with CF**

<table>
<thead>
<tr>
<th>Domain</th>
<th>CFQ-R Child mean score ± SD</th>
<th>CFQ-R Teen mean score ± SD</th>
<th>CFQ-R Parent mean score ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>71.21 ± 23.93</td>
<td>63.02 ± 20.47</td>
<td>59.84 ± 15.15</td>
</tr>
<tr>
<td>Emotion</td>
<td>85.89 ± 10.76</td>
<td>73.16 ± 8.73</td>
<td>76.36 ± 16.96</td>
</tr>
<tr>
<td>Treatment</td>
<td>82.82 ± 17.47</td>
<td>38.89 ± 29.10</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory</td>
<td>66.67 ± 11.12</td>
<td>59.52 ± 21.75</td>
<td>-</td>
</tr>
<tr>
<td>Digestive</td>
<td>76.67 ± 22.50</td>
<td>90.28 ± 12.51</td>
<td>-</td>
</tr>
</tbody>
</table>
P4568 Pulmonary function and quality of life in children and adolescents
adenovirus bronchiolitis obliterans
Stefaníe Nayar1, Ana María Escobar, Monica Saavedra, Alberto Vidal1
Broncopulmonar, Hospital Roberto del Río, Region Metropolitana, Santiago, Chile

Introduction: There are few studies assessing pulmonary function and quality of life of PIBO patients.

Objective: Assess the pulmonary function and the quality of life of patients with PIBO and the correlation between both variables.

Methods: 14 Children with PIBO in follow up at the pediatric pulmonology, were included in this study. Study period: April 2009 - April 2010. Pulmonary function was assessed with spirometry, flow/volume curve and intrathoracic gas volume. A survey of self-administered Quality of Life was applied at the visit to investigate their global, physical and psychosocial quality of life. The Pearson linear correlation between quality of life and the pulmonary function test parameters was assessed, for statistical analysis p<0.05 was considered significant.

Results: The mean age of our patients was 12.4. The functional alterations were characteristics of an obstructive respiratory disorder in 85.7% and only 14.3% showed normal pulmonary function of the patients. The quality of life parameters were in average 58.6% of overall quality of life, 60.9% of physical quality of life and 57.9% of psychosocial quality of life. We found a positive correlation between global quality of life and VEF1, FVC and FEF25-75% (correlation index 0.54, 0.53 and 0.53 respectively) as well between physical quality of life and VEF1, FVC, FEV1/FVC and FEF25-75% (correlation index 0.86, 0.81, 0.70 and 0.74 respectively).

Conclusions: Most patients with PIBO showed pulmonary function impairment characterized by an obstructive respiratory pattern. Better quality of life correlates with better values in spirometric parameters.

P4569 Obliterative bronchitis verified by bronchoscopec visualisation
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Background: Chronic bronchial obstruction in children is mostly associated with bronchial asthma. In those with irreversible obstruction the most documented reason is a post-infectious obliterative bronchiolitis.

Case history: We report a 13 years old patient with Tetralogy of Fallot corrected at the age of 3 years. She suffered from respiratory infections since early childhood, in addition four pneumonias at the age of 10, 11 and 12 years. Since age of 10 on anti-asthma medication for frequent wheezing. She was referred to us for poor response to anti-asthma therapy.


Using 2 mm flexible bronchoscope and aiming for the areas with prominent air-trapping, we found at the level of 7th to 9th bronchial branching circular narrow stenoses and obliterative lesions completely closing the lumen. Biopsy revealed normal bronchial epithelium, mild thickening of the basement membrane and mild hypertrophy of smooth muscle.

Conclusion: We confirmed existence of obliterative lesions causing irreversible obstruction in the bronch of about 2 to 3 mm in diameter. This fits into the diagnosis of obliterative bronchitis, different from obliterative bronchiolitis. This should be suspected in children with irreversible bronchial obstruction and appropriate investigations initiated. Confirmation of this diagnosis can prevent patients from unnecessary burden of anti-asthma therapy.

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effect of hypoxia on otoacoustic emissions findings was found (p<0.05). However, there was no significant effect of inhaled aminoglycosides on auditory functions whether pure tone audiometry, speech audiometry and transient evoked otoacoustic emissions testing. 

Conclusions: Children with chronic lung diseases are liable to cochlear dysfunction due to prolonged hypoxia. Inhaled aminoglycosides in chronic lung diseases is relatively safe on auditory functions. 

P4573 Health-related quality of life in non-cystic fibrosis bronchiectasis children Ameer Hamzah1, Yasemin Gökdemir2, Cagatay Cimis3, Refika Ersu3, Fazilet Karakoc4, Bülent Karadag4, 1Department of Paediatrics, Marmara University Faculty of Medicine, Istanbul, Turkey; 2Department of Paediatric Pulmonology, Marmara University Faculty of Medicine, Istanbul, Turkey; 3Department of Radiology, Marmara University Faculty of Medicine, Istanbul, Turkey; 4Department of Radiology, Marmara University Faculty of Medicine, Istanbul, Turkey

Aim: Bronchiectasis is still an important problem in developing countries. The aim of this study was to evaluate the health-related quality of life and associated factors in children with non-cystic fibrosis bronchiectasis.

Methods: Children with non-cystic fibrosis bronchiectasis followed at Marmara University Paediatric Pulmonology Clinic were included to the study. Age of symptom onset, age of diagnosis, frequency of presenting symptoms, physical examination findings, pulmonary function tests, and affected lobes in high resolution computed tomography (HRCT) were evaluated; in addition, HRCT was scored according to modified Bhalla score system to obtain a bronchiectasis distribution severity score. St George’s Respiratory Questionnaire (SGRQ) and the Medical Outcomes Study Short Form-36 were completed by patients and parents.

Results: The median age of the patients (48.9% male) was 12.1 years (25%-75%: 10.2-14.1years). The median age at diagnosis was 7 years (25%-75%: 5-10years) and follow up period was 4 years (25%-75%: 2-5 years). The patients’ HRCT score did not correlate with the SGRQ scores or FEV1 (p>0.05). However, a significant correlation was found between the SGRQ scores and FEV1 (p=0.02). No correlation was found between SF-36 and FEV1 (p=0.05).

Conclusion: Patients with worse pulmonary functions have lower quality of life scores. Early diagnosis and treatment may increase the quality of life and survival of patients with bronchiectasis, which has irreversible and progressive complications if untreated.

P4574 Pediatric tracheostomy: Indications and complications rate. An experience from a semi-intensive pediatric respiratory unit Alessandra Schiavino, Francesco Paolo Rossi, Maria Giovanna Paglietti, Maria Beatrice Chiariin Testa, Teresa Salerno, Renato Cutrera. Department of Pediatrics, Respiratory Unit, Bambino Gesù Children Research Hospital, Rome, Italy

Tracheostomy in children can be used to provide respiratory support as a long-term ventilation/pulmonary toilet, or to bypass proximal airway obstruction. Tracheostomy is burdened by early and late complications which could make difficult hospital and home management. We performed a single centre Survey from September 2008 to September 2010, identifying early and late complications with the aim to assess the most frequent problems related to tracheostomy management in children. We administered to the parents a questionnaire in which the different topics were addressed (indications to tracheostomy, operational technique, occurrence of intraoperative, early postoperative (within 24 - 48 hours) and late (after 48 hours) complications and the home care management).

In the 2 years period we evaluated 66 patients (M/F 36/30, mean age 7 years). Indications to tracheostomy were prolonged endotracheal intubation followed by tracheal stenosis, chronic respiratory failure, central apnoeas and vocal cord paralysis. Patients were affected by genetic or metabolic disorders, cerebral palsy, neuromuscular diseases, congenital heart diseases, tracheal diseases and tumors of the nervous system.

In 65% of cases no complications occurred, while in 5% early complications and in 35% late complications occurred. Only 4 patients died during the Survey period, but not due to tracheostomy complication. Tracheostomy allows to manage different severe disease in children. The indications for its use have changed over the past decades. Late-onset complications are the most frequent and their knowledge allows to manage the tracheostomized patient from hospital staff and home caregivers.

P4575 Comparison of conventional chest physiotherapy and high-frequency chest wall oscillation in primary ciliary dyskinesia Yasemin Gökdemir, Refika Ersu, Bülent Karadag, Fazilet Karakoc. Paediatric Pulmonology, Marmara University, Istanbul, Turkey

Background: Early diagnosis and enhancement of mucusclearance by chest physiotherapy is important to prevent the development of bronchiectasis in primary ciliary dyskinesia (FSD). Percussion and postural drainage are the most commonly used methods. Vest® is a new chest physiotherapy method which creates oscillation on the chest wall and move the secretions from small airways to the large airways. There is no study evaluating the efficacy of Vest® in FSD. The aim of this study was to evaluate the efficacy and safety of Vest® in FSD patients.

Material/methods: Both conventional chest physiotherapy and Vest® were applied randomly to 7 FSD patients older than 6 years of age. Oxygen saturation was monitored and pulmonary function tests (PFT) were performed on the first and 5th day of both therapies. Patients were questioned about the efficiency and comfort level of the both methods.

Results: Forty-two percent of patients were mean. Mean age was 9.3±3.4 years and the patients were followed up for 7.2±2.3 years. Dextrocardia was present in all of the patients and situs inversus totalis was observed in 71%. There were no desaturation during sessions. Although day 5 PFT were better in both groups, this did not reach statistical significance. There was no difference between the two groups in terms of PFT. Both physiotherapy methods were found effective and comfortable and there was no significant difference between the two groups.

Conclusion: Vest® was comfortable and tolerated well by the patients. There was no difference in PFT’s between the conventional chest physiotherapy and Vest® group. We presented the preliminary results of ongoing the study.

P4576 Impact of the date of diagnosis on the clinical course of children with primary ciliary dyskinesia Folke Brinkmann, Nico laus Schwerk, Theresa Emmrich, Gesine Hansen. University Children’s Hospital, Department of Pulmonology, Allergology and Neonatology, Hannover Medical School, Hanover, Germany

Objective: To up to now, little is known about the impact of the date of diagnosis on the clinical course of children with primary ciliary dyskinesia (pcd).

Methods: Over a ten year period all paediatric patients with confirmed pcd in our tertiary centre who had been followed up for more than 12 months were retrospectively included in the study.

Results: Out of 19 patients 63% had a situs inversus, the median age a diagnosis was 95 months. There was a significant correlation between the date of diagnosis and development of bronchiectasis (p=0.04), but no effect on lung function. 12 months after diagnosis 75% of patients received professional physiotherapy, 88% were on continuous antibiotic therapy, 50% on inhaled β agonists and 13% on continuous inhaled corticosteroids. After starting the treatment, all patients improved clinically, the number of pulmonary complications decreased, especially pneumonias (p=0.03) and bronchitis (p=0.01). Chronic wet cough and rhinitis often persisted and lung function measurements did not improve permanently.

Conclusions: Late diagnosis of pcd carries an increased risk for developing bronchiectasis. Pulmonary exacerbations decrease with appropriate treatment whereas there is no significant effect on lung function parameters.

P4578 The follow-up of children with tracheobronchial foreign body aspiration Sinan Tas1, Zeynep Seda Uyar2, Nihat Uyar2, Yonca Anik3, Tuha Liman4, Metin Aydogan5, Salih Topcu5, Emin Sarit Aksit6. 1Pediatrics, Kocaeli University Hospital, Kocaeli, Turkey; 2Pediatric Pulmonology, Kocaeli University Hospital, Kocaeli, Turkey; 3Radiology, Kocaeli University Hospital, Kocaeli, Turkey; 4Thoracic Surgery, Kocaeli University Hospital, Kocaeli, Turkey; 5Pediatric Allergology, Kocaeli University Hospital, Kocaeli, Turkey; 6Pediatric Infectious Diseases, Kocaeli University Hospital, Kocaeli, Turkey

Background: Foreign body aspiration (FBA) is an important cause of morbidity and mortality in children

Objectives: Retrospective analysis of cases who arrived Kocaeli University Hos pital with suspected FBA and underwent bronchoscopy

Methods: Forty children who underwent bronchoscopy for FB removal from February 2005 to January 2010 at Kocaeli University Hospital were reviewed retrospectively. We recorded the patients’ presenting symptoms,physical and radiological findings, the time elapsed from aspiration to presentation,type and location of FBA,acute and long-term complications, follow up period and hospitalisation period

Results: There were 26 male patients. The mean age was 59.8±34.2 months (range 29-195 months).FBs were removed within 1-184 days following the aspiration (median: 2 days).During presentation;38 cases had clinical symptoms and wheezing was the most common one. Thirty-three FBs were organic and hazelnuts were the most common. Twenty-three (57.5%) cases had radiological findings during presentation and 10 (25%) had acute complications (pneumonia). Patients were hospitalized for 1-17 days (median 2days) and followed up for 34.5±31.3 months. Seventeen patients had persistent clinical symptoms. There were chronic radiological findings in 5 patients and fibrotic sequelae in 11 patients. Although statistically not significant; chronic radiological findings were more common in patients in whom bronchoscopy was performed later.

Conclusions: Follow up period and methods of children with tracheobronchial FBA are controversial. Additionally, there are not enough studies about its long term complications. Some patients cannot be followed up for a sufficient period and this lead to the development of chronic complications.
Background: Bronchiolitis obliterans (BO) is an uncommon and severe form of chronic obstructive lung disease in children that results from an insult to the lower respiratory tract. The aim of this study was to evaluate the respiratory symptoms of BO patients and determine related factors.

Methods: Retrospective evaluation of BO patients who were followed-up from pediatric pulmonology department.

Results: Total of 22 patients (65% male) were included to the study. Mean age was 9.1±3.8 years. During first lower respiratory tract infection, mechanical ventilation and O2 was required in 32% and 9% of patients, respectively. Eighty percent of patients were treated with inhaled or oral steroids in the early period. Respiratory symptoms were recurrent in 35% and persistent in 65% of patients after the first lung infection. The age of 11 (50%) patients were above six currently percent of patients were treated with inhaled or oral steroids in the early period. Lobectomy was performed in one patient. Four (18%) patients were using O2 and one patient was using non-invasive ventilation (NIV) at the last visit. The rate of intubation during the first lung infection was 80% in the patients who required respiratory support in the follow-up period. There was a significant relationship with intubation during the first lower respiratory infection and requirement of O2 versus NIV (p=0.001) in the follow-up period.

Conclusion: BO is a disease of childhood with high morbidity and mortality. The severity of the respiratory symptoms of patients during follow-up is associated with the requirement of mechanical ventilation during the first lower respiratory infection.

649. Lung cell injury and repair

P4582
Down-regulation of SLPI by cysteinyl leukotrienes in human bronchial epithelial cells can be reverted by glucocorticoids

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Secretory leukoproteinase inhibitor (SLPI) protects the lung against proteinases implicated in the pathogenesis of diseases like COPD, but has also antimicrobial and anti-inflammatory properties. A fall in SLPI contents in the airways has been detected in COPD and asthma, however, the factors involved in the regulation of SLPI gene expression in the airway epithelial cells have insufficiently studied.

To evaluate whether pro-inflammatory cysteinyl leukotrienes (CysLT) exert regulatory effects on SLPI expression in normal human bronchial epithelial cells, the cultured cells were exposed to 0-50 nM LTE4 for 3-6 h. Expression of SLPI mRNA was analyzed by RT-qPCR. The potential of glucocorticoids (GC) to revert the CysLT-induced effect on SLPI expression was addressed by incubating the cells for additional 3 h with 10 nM fluticasone propionate (FP) and 20 nM budesonide (BUD). Montelukast at 106 mol/L was used to block the possible CysLT-mediated action of LTE4.

Exposure of the cells to 50 nM LTE4 resulted in a significant drop in SLPI expression after 6 h (p<0.001). Both GC alone tended to increase the expression of SLPI. More importantly, in the cells exposed to LTE4, both FP and BUD fully reverted the CysLT-induced drop in SLPI (p<0.001 and p<0.003, respectively). The presence of montelukast did not additionally influence the potency of GC.

In conclusion, by down-regulation of SLPI in bronchial epithelial cells, CysLT may augment the pathogenetic events leading to COPD providing a pathway for more rapid decline in lung function in COPD patients with a concomitant Cyst-MT-mediated disorder like asthma. Fortunately, this can be overpowered by treatment with GC.

P4583
Identification of mesenchymal stem cellstromal cells in lung tissue from lung-transplanted patients

Sara Rolandsson1, Annika Andersson-Sjöland 1, Jan Claas Brune2.

Leif Eriksson1, Stefán Scheding3,4, Leif Björmer1, Gunilla Westergren-Thorsson1. 1Experimental Medical Science, Lung Biology, Lund, Sweden; 2Lund Stem Cell Center, Laboratory Medicine, Lund, Sweden; 3Clinical Medical Sciences, Lung Medicine and Allergology, Lund, Sweden; 4Hematology, Laboratory Medicine, Lund, Sweden

Background: Multipotent mesenchymal stromal cells (MSC) have been isolated from a variety of human tissues. Previous studies have shown that MSC are present in the bronchoalveolar fluid from lung-transplanted patients where they were suggested to be an indication of a future bronchiolitis obliterans syndrome (BOS) onset. We hypothesize that MSC are lung-resident cells that are present in lung tissue from lung-transplanted patients.

Objective: Our aims were to examine whether MSC are present in lung tissue from lung-transplanted patients and to evaluate whether these cells showed typical MSC characteristics such as adherent clonal growth and multi-lineage differentiation capacity.

Methods: MSC were isolated from central- and distal biopsies obtained from lung-transplanted patients (3 mo. – 13 yrs. post transplantation). After dissociation, the resulting single cell suspension was subjected to colony-forming unit-fibroblast (CFU-F) assays to determine the frequency of mesenchymal progenitor cells. Further, the cells were assayed for their differentiation capacity towards adipocytes, chondrocytes and osteoblasts. The surface marker profile of lung-derived MSC was examined by flow cytometry.

Results: MSC isolated from lung tissue adhered to tissue culture treated plastic, formed colonies when cultured in CFU-F assays and possessed multi-lineage potential. Immunophenotyping showed that lung-derived MSC were positive for the surface markers such as CD73, CD90 and CD105 and negative for CD45 and CD34.

Conclusion: Our study suggests that there are MSC present in the lung tissue of lung-transplanted patients that possess multi-lineage potential and give rise to typical colonies in vitro.
Lung on Chip: In vitro HGF effects on injured alveolar A549 epithelial cells in microfluidic system

Pauline Salin1,2, Laurent Barbe1,3, Amig Gazdar2, Thomas Geiser2, Oliver Guenta1,3, 1 CSEM, CSEM Centre Suisse d’Electronique et de Microtechnique, Landquart, Switzerland; 2Division of Pulmonary Medicine, University Hospital Bern, Bern, Switzerland; 3ARTORG, University of Bern, Bern, Switzerland

Microfluidic systems have become competitive tools in the in vitro modelling of diseases and promising alternatives to animal studies. They allow more invivo like conditions for cellular assays. Research in idiopathic pulmonary fibrosis could benefit from this novel methodological approach to understand the pathophysiology of the disease and develop efficient therapies. The use of hepatocyte growth factor (HGF) for alveolar reepithelisation is a promising approach. In this study, we show a new microfluidic system to analyse the effects of HGF on injured alveolar epithelial cells. Microfluidic systems in polydimethylsiloxane were fabricated by soft lithography. The alveolar A549 epithelial cells (10,000 cells) were seeded and studied in this microfluidic systems with media perfusion (4μl/min). Injury tests were made on the cells by the perfusion with media containing H2O2 or bleomycin. The degree of injury was then assessed by a metabolic and an apoptotic assays. Wound assays were also performed with a central laminar flow of trypsin. Monitoring of wound closure with HGF vs control media was assessed. The alveolar A549 epithelial cells grew and proliferated in the microfluidic system. In the wound closure assay, the degree of wound closure after 5 hours was 53.3%±1.3% with HGF compared to 9.8±2.4% without HGF (P<0.001). We present a novel microfluidic model that allows culture, injury and wounding of A549 epithelial cells and represents the first step towards the development of an invivo reconstitution of the alveolar-capillary interface. We were also able to confirm that HGF increased alveolar epithelial repair in this system.

Lung on Chip: Co-culture of alveolar epithelial cells & bone marrow derived stromal cells in microfluidic system

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Background: Microfluidics system are novel tools to study cell-cell interactions in vitro. This project focuses on the development of a new microfluidic device to co-culture alveolar epithelial cells and mesenchymal stem cells to study cellular interactions of the injured alveolar epithelium. Methods: Microfluidic systems in polydimethylsiloxane were fabricated by soft lithography. The alveolar A549 epithelial cells were seeded and injury tests were made on the cells by perfusion with media containing H2O2 or bleomycin during 6 or 18hrs. Rat Bone marrow derived stromal cells (BMSC) were then introduced under constant perfusion. Epithelial injury to mimic mechanisms seen in idiopathic BMSC adhered to the bottom surface of the microfluidic device and proliferated. P4586 BMSC, and showed that BMSC try to heal the injured epithelium. Also we were able to confirm that HGF increased alveolar epithelial repair in this system.

P4586

Lung on Chip: Co-culture of alveolar epithelial cells & bone marrow derived stromal cells in microfluidic system

Patricia Leon1, Xu Shi-Wen2, Carmel Stock1, David Abraham3, Andrew Nicholson2, Toby Maher1, Athol Wells2, Elizabeth Renzoni1, Gisela Lindahl1, 1Intestinal Lung Disease Unit, Royal Brompton Hospital, London, United Kingdom; 2Department of Rheumatology, Royal Free Hospital, London, United Kingdom; 3Department of Histopathology, Royal Brompton Hospital, London, United Kingdom

Background: In our microarray study of lung fibroblasts from control subjects (n=10) and patients with scleroderma-associated interstitial lung disease (SSc-ILD) (n=8), the Interferon Stimulated Genes (ISGs) are an overrepresented group of genes with reduced expression in SSc-ILD fibroblasts. Since interferon gamma is known to interfere with TGF-β signalling and reduce the expression of individual pro-fibrotic genes, we asked whether TGF-β signalling could in turn downregulate ISG in lung fibroblasts, and whether TGF-β could affect the induction of ISGs by interferons. In this study, we have focused on the expression of IRF-1, a key transcription factor regulating ISGs. Methods: Human primary pulmonary fibroblasts were grown to near confluence, serum starved in 0.1% BSA for 24 hrs, and treated with or without TGF-β (2ng/ml), IFNα (250ng/ml), and IFNγ (10ng/ml), for a further 24 hrs. Specific antibodies were used to assess protein expression in cell layers by Western blot analysis.

Results: IRF-1 mRNA expression was significantly reduced in SSc-ILD fibroblasts (-3.6-fold, p=0.0001). TGF-β treatment suppressed basal IRF-1 protein expression to undetectable levels in fibroblast preparations from control and SSc-ILD lungs. In both SSc-ILD and control fibroblasts, TGF-β had no effect on IFNβ-induced IRF-1 protein expression, but completely inhibited the induction of IRF-1 by IFNα. By contrast, IFNγ reduced TGF-β induced CTGF expression, while IFNα had no effect. Conclusion: TGF-β signalling suppresses basal and IFNα-induced IRF-1 expression in lung fibroblasts, suggesting a possible mechanism for the reduced expression of ISGs expression observed in SSc-ILD fibroblasts.

Alveolar lymphocyte phenotype and respiratory distress syndrome

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Introduction: The role played by adaptive immunity in the pathophysiology of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is largely unknown. We characterized lymphocytes phenotype in broncho-alveolar lavage (BAL) during respiratory distress syndromes. Patients and method: Analyses were carried out on BAL samples of three patients groups: ALI/ARDS patients (ARDS group), healthy patients (control group) and inflammatory pulmonary diseases patients (ID group). Lymphocyte and monocyte/macrophage phenotype determination used cytometric fluorescence techniques: CD45RA+, CD45RA- and CD25FoxP3 cells were respectively identified as naive, memory and regulatory T cells. HLAD, KI67 and annexin V were used as markers for cell activation, proliferation and apoptosis respectively. CD4, CD8, CD3, CD20, CD69, CD28, CD40/CD40L and CTLA-4 were used as costimulator markers. Results: 9 BAL were obtained from 8 ARDS patients, 8 BAL from controls and 8 from ID patients. A significant increase of HLAD, KI67 and CTLA-4 on T CD4+ lymphocytes was observed in ARDS group compared to control. Concerning CTLA-4, the difference still persisted when comparing ID to ARDS group. KI67 expression was significantly increased on T CD8+HLA-DR and TDB6 were significantly decreased on alveolar macrophages (AM) compared to others groups. Discussion: During ALI/ARDS activation and proliferation of T lymphocyte are noticeable, associated with alteration of the CD28/CTLA-4 costimulator pathway and ligand on AM. Conclusion: This is the first human study on adaptive immunity in ARDS/ALI identifying relevant modifications on T cell phenotype which may account for the dramatic alveolar inflammation observed in these syndromes.

IL-18 and IL-12 induce inflammatory cytokines, chemokine ligand 9 (CXCL9) and T cell infiltration in pulmonary tissue

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Background: Increased levels of interleukin (IL)-18 and IL-12 have been found during experimental alveolar hypoxia and in patients with COPD. Aims: To study the presence of IL-18 and IL-12 receptors (IL-18R/IL-12R) in the lungs and the effect of IL-18 and IL-12, alone or in combination, on the lungs with regard to inflammatory response and induction of emphysema related metalloproteinases (MMP2, MMP9, MMP12). Methods: Expression of IL-18R and IL-12R was studied in lungs, heart, liver and spleen in C57Bl/6 mice. 24 hours after a single i.p. dose of recombinant murine IL-18 alone, recombinant IL-12, IL-18+IL-12 or PBS (controls), lungs were harvested for immunohistochemical (IHC) and RT-PCR analyses. Results: The expression of IL-18R mRNA was 16-630-fold higher in the lungs than in other organs. The expression of IL-12R was 4-fold higher in the spleen than in lungs. Mice treated with IL-18 or IL-12 alone showed significantly higher mRNA levels of interferon-γ, tumor necrosis factor-α and MMP12, than in controls (p<0.05). Mice treated with IL-18+IL-12 showed an even more pronounced induction of these mediators, as well as a significant increase in IL-6 and IL-1β(p<0.05). A marked increase in CXCL9 mRNA was induced by IL-18 (12-fold), IL-12 (19-fold), IL-18+IL-12 (153-fold). IHC showed perivascular T-cell infiltration following co-stimulation. Conclusions: High levels of IL-18 receptor suggest that the lungs might be a target organ for IL-18. IL-18+IL-12 exert a synergistic effect on the lungs by inducing inflammatory cytokines and MMP12 which may promote inflammation and emphysema. Induction of CXCL9 may be of importance for the observed T cell infiltration in lung tissue.
Characterization of human mesenchymal stem cells phenotype and secretome in a in vitro model of acute lung injury inflammation

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Intra-tracheal instillation of MSCs may have therapeutic efﬁcacy in models of acute lung injury (ALI). Protective effects of MSC are reported despite low engraftment rates supporting that paracrine mediators may be involved. In ALI MSCs delivered by intra-tracheal route are exposed to alveolar hypoxia and cytokines, both known to independently modify MSC phenotype, which may affect their survival or their reparative properties. We therefore investigated the effects of a typical alveolar ALI microenvironment consisting in hypoxia (HYP) and cytokons (CYT; IL-8, TNFα and IFNγ) on MSC phenotype, apoptosis and secretion profile. Testing the effects of such conditions is important to better understand the fate and behavior of MSC instilled into injured lungs and to detect potential modiﬁcation of their secretion proﬁle. In order to decide whether MSC preconditioning might be an interesting strategy, MSC were exposed 24 hours to CYT 50mg/ml and/or HYP (5% O2). CYT and/or HYP neither modify the expression of the typical MSCs markers (CD90, CD105, CD45) nor the degree of apoptosis necrosis when compared to control MSCs. We measured KGF, PGE2 and IL-1 receptor antagonist (IL-1rA) in the supernatant because they are known to be important for resolution of alveolar edema. We measured KGF, PGE2 and IL-1rA (0 vs 134 ± 26 ng/ml) but decreased by two fold the release of KGF (345 ± 8 vs 115 ± 12.8 ng/ml). In conclusion: Hypoxic and inﬂammatory environment mimicking ALI does not affect the survival and phenotype of MSC but differentially modulates KGF, PGE2 and IL-1rA secretion.

The role of leptin in pulmonary neutrophilia during murine acute lung injury

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Rationale: One of the hallmarks of Acute Lung Injury (ALI) is the extensive recruitment of neutrophils to the lung. Recent evidence shows that leptin expression is increased in the injured human lung, and is known to have diverse effects on leukocytes. We hypothesized that leptin contributes directly to neutrophil recruitment in the lung during ALI.

Methods: C57Bl/6 wild type (WT) mice were examined in a lipopolysaccharide (LPS) model of lung injury with or without oropharyngeal aspiration of recombinant leptin. We measured bronchoalveolar lavage (BAL) neutrophilia, leptin concentrations and inflammatory cytokine levels at 24 hours after injury. In addition, the effects of LPS induced lung injury were examined in leptin resistant (db/db) obese and Diet Induced Obese (DIO) mice and their lean controls. Lastly, we examined chemotaxis to leptin in neutrophils isolated from lean and obese uninjured mice.

Results: BAL leptin levels were significantly increased in injured WT mice (1324 pg/ml ± 320 relative to their saline-treated controls (96 pg/ml ± 74) 24 hours after LPS exposure. Recombinant leptin administration after LPS induced airspace neutrophilia was not effective. LPS exposure in WT mice, yet inflammatory cytokine levels in BAL remained unchanged. In addition, we observed attenuation in BAL neutrophilia in both db/db and DIO obese mice compared to their lean controls. Lastly, neutrophils were found to migrate to leptin in vitro, and obesity blunted this response.

Conclusion: Our ﬁndings indicate that leptin plays a role in neutrophil recruitment to the lung during ALI. This appears to occur in part via leptin-induced neutrophil chemotaxis, which is diminished in obesity.

Preferential activation of alveolar macrophages versus epithelial cells during initiation of ventilator-induced lung injury in mice

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Background: It has been suggested that stretch-induced deformation of alveolar epithelial cells (AEC) plays a role in the initiation of ventilator-induced lung injury (VILI). In vitro stretch of AEC upregulates intracellular mitogen-activated protein kinases (MAPK) leading to mediator release, but this may not reﬂect the situation in vivo. We have developed a novel method to measure MAPK intermediates within discrete lung cell populations following in vivo VILI.

Methods: Anaesthetised C57Bl6 mice were ventilated with high (V=40ml/kg) or low stretch (V=10ml/kg). At various time points lungs were removed and single cell suspensions were produced by mechanical disruption, with cells immediately ﬁxed and permeabilised. Levels of intracellular phosphorylated (p-) MAPKs and DIO were determined by flow cytometry.

Results: p-ERK and p-MEK2 expression (mean fluorescence intensity, MFI) increased in AM within 5 minutes of high stretch. In contrast, both type I and II AEC showed little p-ERK and p-MEK2 phosphorylation, even up to 1 hour.
Conclusion: Contrary to previous suggestions that stretch-induced activation of AEIC is the key initiator of VILI, our results indicate an immediate, direct activation of AM with high stretch, placing AM as potentially more important than AEIC in triggering the early inflammatory response during VILI.

P4594

Immunomodulatory function of chemerin and its receptor ChemR23 in the pathophysiology of viral pneumonia and acute lung injury

Benjamin Bondue1, Olivier Vosters2, Patricia De Nadai2, Stephanie Glineur4, Daniela Desmecht4, Paul De Vuyst1, Marc Parmentier2.

Viviane Cagido1, Natália Casquilho 1, Douglas Barbosa 1, Raquel Soares 1, Temporal behavior of lung injury induced by instillation of microcystin-LR (MC-LR) in mice. MC-LR mediated by non-leukocytic cells, such as lung endothelial or epithelial cells. Moreover, a strong anti-inflammatory role of chemerin is observed in a model on non-leukocytic cells. Indeed, experiments involving adoptive transfer of pDCs explain the delayed acquired response and viral clearance in ChemR23 -/- mice. However, the stronger inflammation observed in these mice is not due to defective pDC recruitment but rather to the loss of an anti-inflammatory role of chemerin in non-leukocytic cells. Indeed, experiments involving adoptive transfer of pDCs and bone marrow transplantation exclude the role of ChemR23-expressing pDCs and more generally leukocytes in the protection against excessive inflammation. Moreover, a strong anti-inflammatory role of chemerin is observed in a model of acute lung injury induced by instillation of the pneumonia virus of mice (PMV). ChemR23+ mice display delayed viral clearance, and impaired acquired immunity, contrasting with an excessive innate response and recruitment of neutrophils. Lower recruitment of type I interferon-producing plasmacytoid dendritic cells (pDCs) may explain the delayed acquired response and viral clearance in ChemR23 -/- mice. However, the stronger inflammation observed in these mice is not due to defective pDC recruitment but rather to the loss of an anti-inflammatory role of chemerin in non-leukocytic cells. Indeed, experiments involving adoptive transfer of pDCs and bone marrow transplantation exclude the role of ChemR23-expressing pDCs and more generally leukocytes in the protection against excessive inflammation. Moreover, a strong anti-inflammatory role of chemerin is observed in a model of acute lung injury induced by instillation of the pneumonia virus of mice (PMV). ChemR23+ mice display delayed viral clearance, and impaired acquired immunity, contrasting with an excessive innate response and recruitment of neutrophils. Lower recruitment of type I interferon-producing plasmacytoid dendritic cells (pDCs) may explain the delayed acquired response and viral clearance in ChemR23 -/- mice.

P4595

Temporal behavior of lung injury induced by instillation of microcystin-LR in mice

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Cyanotoxins present in the water for human use may yield serious health problems. We aimed to evaluate the effects of microcystin-LR (MC-LR) on lung mechanics, lung and liver histology and inflammation, and oxidative stress. Male Swiss mice (n=149) were randomly divided in 2 groups: control (CT) received sterile saline intratracheally (i.t., 50 μL), and MC a sublethal dose of MC-LR (40 μg/kg, i.t.). CT (n=13), and MC mice were evaluated at 2, 4, 6, 8, 15, 22, 24, 48 h after MC -LR instillation. The amount of polymorphonuclear cells and mesotheliocytosis activity in lung augmented in all MC groups until 96 h, indicating a neutrophilic inflammatory cell infiltrate. Hepatic histology showed necrosis and hepatocyte disarrangement in 8 h. Free MC-LR was detected in lung and liver homogenates, with a time-dependent toxin accumulation in liver. Antioxidative enzymes activities and thiobarbituric acid reactive substances were altered in MC-LR exposed animals. i.t. administration of MC-LR led to a biphasic compromise of pulmonary mechanics: an early deterioration (2 h and 6 h), normalization at 24 h, and a later worsening (48 h). Also, alveolar collapse, lung and liver inflammation, imbalance of antioxidants enzymes, and oxidative damage were identified. This work reinforces the airways as an important route of introduction of MC-LR. Supported by: PRONEX/FAPERJ, FAPERJ, CNPq, MCT

P4596

Toxicological assessment of indoor airborne fine particulate matter induced oxidative stress in alveolar epithelial cells

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Background: Exposure to airborne particulate matter (PM) has long been associated with adverse health problems. These fine PM particles can penetrate the distal regions of the lung causing severe respiratory problems.

Objectives: As relatively little information of indoor fine PM is available to evaluate the actual risks, we will focus our examination on lung injuries caused by fine indoor PM, by investigating the mechanism of the cell injury using primary culture of alveolar type II cells.

Method: Indoor PM was collected in Nara prefecture, Japan using an Andersen sampler by the impactor cascade method. Particle samples of PM were collected on five Teflon filters in accordance with the diameter of particles (diameter: >11μm, 2.1-11.1 μm, 1.1-2.1 μm, 0.1-1.1 μm, <0.1 μm). Alveolar type II cells from rats were exposed to PM at the concentration of 500 μg/ml for 24 hrs respectively. At the end of the experiment, lactate dehydrogenase (LDH) activity released into the culture medium was determined and the percentage of LDH leakage was then calculated to reflect the cytotoxicity of PM.

Results: In relation to the control cells, the PM-induced LDH leakage was more significant among the smaller fine particles of indoor PM than the larger one. However this did not occur with the above mentioned 1.1 μm diameter size of PM. Superoxide dismutase (SOD) significantly reduced LDH leakage induced indoor PM. In the analysis of the elements in indoor PM, the most abundant element was iron (Fe).

Conclusions: Indoor PM causes oxidative cellular damage, which may be closely associated with a transition metal, Fe in rat alveolar epithelial cells.

P4597

Effect of nanoparticle and NO2 exposure on thoracic gas volume in Brown Norway rat

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Rationale: Air pollutant exposure, has been associated with increased asthma morbidity in children. The aim of the present study was to determine whether exposure to NO2 and carbon nanoparticles (CNPs) affect the rate of Thoracic gas volume (TGV) change with growth in 7-week old Brown-Norway (BN) rats.

Methods: Animals were anesthetized and tracheally intubated. TGV was measured using whole-body plethysmography at age 49 days, and following a 4-week exposure to air, NO2 (10 ppm) 5bd, 5wkd, CNP (FW2, Ø 13 nm; 3 instillations at 2, 11 and 24 days). 11 different groups were compared.

Results: TGV significantly increased after 4 weeks in all groups. When normalized to body weight, TGV increased significantly only in the air-exposed group.

MAPK phosphorylation

<table>
<thead>
<tr>
<th>MAPK</th>
<th>AM</th>
<th>Type I AEIC</th>
<th>Type II AEIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-38 (MFI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mins low</td>
<td>4.1±1.9</td>
<td>0.7±0.4</td>
<td>4.0±0.2</td>
</tr>
<tr>
<td>5 mins high</td>
<td>12.8±1.0</td>
<td>1.4±0.4</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>p-MK2 (MFI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mins low</td>
<td>23.1±4.9</td>
<td>15.6±3.9</td>
<td>18.6±5.1</td>
</tr>
<tr>
<td>5 mins high</td>
<td>35.4±5.3</td>
<td>20.8±5.7</td>
<td>21.4±5.5</td>
</tr>
</tbody>
</table>

Mean ± s.d.; *p<0.05, **p<0.001 by t-test; N=3-4.

Data are mean ± SD; *p<0.05 vs. control; **p<0.05 vs. Air; #p<0.05 vs. NO2, by one-way ANOVA. MC by MLK.

Conclusions: These data show that a 4-week exposure to either NO2 or CNP significantly decreases TGV and the rate of TGV increase with age in BN rat, suggesting a reduced lung growth rate. CNP, NO2 and combined exposure produced distinct lung inflammatory cytotoxic profiles.
P4598

A new method for detection of flow limitation in COPD using dynamic chest X-ray examination
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Purpose: Spirometry which requires maximum effort tasks COPD patients. In this study, we proposed a new method for detection of flow limitation without effort breathing.

Subjects: Dynamic chest X-ray from 10 normal volunteers, 16 mild COPD patients (GOLD Stage I or II) and 12 severe COPD patients (GOLD Stage III or IV) were obtained in the upright position in about 10 seconds of tidal breathing at rest. The dynamic image data captured at 7.0 frames per second was synchronized with the pulsed X-ray. The institutional review board approval and written informed consent were obtained in all persons.

Methods: We calculated the maximal differential values in each ventilation phase at the corresponding small local area of lung in the series of dynamic chest X-ray. The regional relative flow rate ratio was obtained from the peak values of inspiratory phase divided by the peak values of expiratory phase. All groups were compared about the average of flow rate ratio.

Results: The regional changes in inspiratory/expiratory flow rate ratio had larger values and broader distribution in COPD patients than those of normal volunteers. The average of the ratio in normal volunteers, in mild COPD patients and in severe COPD patients were 1.04±0.09, 1.17±0.08, and 1.19±0.13 (mean±SD), respectively. A significant difference was confirmed between the normal volunteers and the COPD patients (p=0.031).

Conclusion: The inspiratory/expiratory flow ratio rates in COPD patients were higher than those of healthy volunteers. The new method for ventilation function has possibility to evaluate flow limitation without effort breathing.

P4599

Gravity dependence of lung density and specific gas volume (SVg) assessed by CT in health and emphysema
Francesca Pennati1,2, Caterina Salito1,2, Jason Woods4,5, Peter Macklem4,5, Andrea Aliverti1,2, Dip. di Bioingegneria, Politecnico di Milano, Milano, Italy; 2Dept. of Radiotherapy and Physics, Washington University, St. Louis, United States; 3Health Centre Research Institute, McGill University, Montreal, Canada

Introduction: Lung density and SVg variations between different lung volumes are reliable estimates of regional lung emptying/filling (Salito et al.,Radiology,2009). Here the gravity-dependent regional differences occurring within the lung in both healthy (H) and emphysema (E) is evaluated.

Methods: 10 healthy volunteers and 10 subjects with severe emphysema (FEV1<50%pred, RV/TLC>0.65) were acquired at TLC and RV via static high-resolution-CT. For each subject, three levels, aortic arch (AA), carina (C) and top diaphragm (TD), were chosen to register through an optical-flow-based method the RVslice to the correspondent TLC one. Pixel-by-pixel differences between TLC and RV of healthy patient and emphysema were calculated. Frequency distribution plots of ΔSVg at the different levels were then expressed in terms of mean, median, standard deviation and skewness.

Results: Table 1 reports the pertinent values of the frequency distribution of ΔSVg in healthy and COPD subjects for each tracheo-bronchial tree level.

<table>
<thead>
<tr>
<th>Population</th>
<th>Health</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>AA</td>
<td>C</td>
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<tr>
<td>Mean (ml/g)</td>
<td>5.0±1.1</td>
<td>5.0±1.0</td>
</tr>
<tr>
<td>Median (ml/g)</td>
<td>4.8±1.1</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>Standard Deviation (ml/g)</td>
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<td>2.9±0.8</td>
</tr>
<tr>
<td>Skewness (ml/g)</td>
<td>1.1±0.9</td>
<td>1.0±1.3</td>
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</table>

*p<0.01 vs healthy.

Conclusions: In severe emphysema, ΔSVg is smaller at any lung level, suggesting that alveolar destruction and gas trapping are homogenously distributed within the lung. Regional distribution of SVg in emphysema presents an high degree of heterogeneity respect to healthy.

P4600

Lung structure in healthy nonsmokers and smokers assessed by CT-densitometry and chest X-ray
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Background: Smoking causes inflammation in the lungs, which may lead to structural changes and irreversible airways obstruction, characteristic for COPD. By computed tomography (CT), areas with Hounsfield units (HU) below -900 have been considered as emphysema, while increased attenuation may indicate inflammation. We investigated changes in smokers compared to neversmokers.

Materials and methods: 40 current smokers (35±12 pack-years, mean±SD) with normal lung function and 36 healthy nonsmokers performed chest X-ray and CT. Age was 45-65 years with equal sex distribution. Lungs were defined as voxels with attenuation between -300 to -1024 HU, further divided into eight intervals. Chest X-rays were evaluated according to criteria's: depression of the diaphragm, irregular radiolucency, abnormal retrosternal space and sternodiaphragmatic angle >90°. Two or more criteria's was considered as emphysema.

Results: Mean lung attenuation in smoking (±854HU±13; mean±SD) and female smokers (±854HU±19) was higher than in nonsmokers (male -880HU±20; females -872HU±18) (p<0.05 for both). In women, the percent of areas with HU below -950 was lower in smokers than nonsmokers (p<0.001), the difference was smaller in men (p<0.05). Chest X-ray detected emphysema in 22% of male and 15% of female smokers, but in none of the neversmokers.

Discussion: Increased lung density in smokers may indicate inflammation but this may be to correlated to other signs of local inflammation. Females may be more vulnerable than males to the effects of smoking. Despite normal lung function, a considerable number of subjects had emphysema on plain chest x-ray. Further analyses are in progress including patients with COPD.

P4601

Specific gas volume (SVg) variations between different lung volumes in health and emphysema
Francesca Pennati1, Caterina Salito1, Jason Woods4,5, Peter Macklem4,5, Andrea Aliverti1,2, Dip. di Bioingegneria, Politecnico di Milano, Milano, Italy; 2Dept. of Radiology and Physics, Washington University, St. Louis, United States; 3Health Centre Research Institute, McGill University, Montreal, Canada

Introduction: Variation of specific gas volume (SVg) between high and low lung volume is a reliable estimate of regional lung filling/emptying (Salito et al.,Radiology,2009). The aim of this study was to evaluate how these variations are distributed in different regions of the lung in healthy and COPD subjects.

Methods: 10 healthy volunteers and 10 subjects with severe emphysema (FEV1<50%pred, RV/TLC>0.65) were scanned at TLC and RV via static high-resolution-CT. For each subject, three levels, aortic arch (AA), carina (C) and top diaphragm (TD), were chosen to register through an optical-flow-based method the RV slice to the correspondent TLC slice. For each level pixel-by-pixel SVg differences between TLC and RV (ΔSVg(TLC)-SVg(TD)) were calculated. Frequency distribution plots of ΔSVg at the different levels were then expressed in terms of mean, median, standard deviation and skewness.

Results: Table 1 reports the pertinent values of the frequency distribution of ΔSVg in healthy and COPD subjects for each tracheo-bronchial tree level.

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*p<0.01 vs healthy.

Conclusions: In severe emphysema, ΔSVg is smaller at any lung level, suggesting that alveolar destruction and gas trapping are homogeneously distributed within the lung. Regional distribution of SVg in emphysema presents an high degree of heterogeneity respect to healthy.

P4602

Gender and age related changes in upper airway morphology in a population of obese/OSA children
Wim Vog1, Stijn Verhulst2, Jan De Backer1, Kim Van Hoorenbeeck2, Wilfried De Backer1, 1Respiratory, FluidAir no; Kontich, Belgium; 2Pediatrics, University Hospital Antwerp, Edegem, Belgium; 3Respiratory Medicine, University Hospital Antwerp, Edegem, Belgium

Introduction: This study aims to investigate the gender and age related changes in upper airway morphology in a population of obese/OSA children.

841s
**P4603**

Airway dimensions in COPD patients: Relationship with lung functions
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**Background:** There is growing attention about evaluating the airway abnormality in chronic obstructive pulmonary disease (COPD) using airway dimensions.

**Objective:** To investigate relationship between airway dimensions measured by multi-slice spiral CT (MSCT) and lung functions in COPD patients.

**Methods:** 25 COPD patients and 15 healthy subjects underwent MSCT scans and pulmonary function test. The airway wall thickness (T) and airway luminal area (Ai) of apical bronchi of the right upper lobe in the CT images were measured. The ratio of T and the total diameter (T/D) and percentage of airway wall area to outer area (WA%) of the bronchus were calculated from T and Ai. Ventilation function, lung volume, airway resistance and diffusion function were detected in pulmonary function test.

**Results:** There were significant differences between COPD patients and healthy subjects in T/D, Ai/BSA and WA%.

<table>
<thead>
<tr>
<th>COPD patients</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/D</td>
<td>0.3±0.05</td>
</tr>
<tr>
<td>Ai/BSA</td>
<td>4±2</td>
</tr>
<tr>
<td>WA%</td>
<td>81.1±8.1</td>
</tr>
</tbody>
</table>

**Conclusions:** Airway dimensions measured by MSCT correlated strongly with lung functions and provided large amount of information about the airway abnormality in COPD.

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**P4604**

Bone mineral density (BMD) in male patients with chronic obstructive pulmonary disease (COPD) in age 40-70 years
Sviatlana Lemiasheuskaya, Alexander Makarevich, Alla Shepelkevich. Internal Medicine, Belarusion State Medical University, Minsk, Belarus

**Background:** COPD is often associated with the systemic extra pulmonary effects such as osteoporosis.

**Aim and objectives:** To study the dynamics of BMD in the course of COPD progression.

**Material and methods:** We examined 72 COPD male patients (aged 40-70 years). The COPD pts were subdivided into groups according to COPD severity: the 1st was made of 14 men; GOLD I stage; mean age 55 years; FEV1 78%; BMI 27 kg/m², smokers 68%, paquets/ys 20; the 2nd included 43 patients; GOLD II stage; mean age 57; FEV1 65%; BMI 28 kg/m², smokers 80%; paquets/ys 21; the 3rd -20 patients; GOLD III stage; mean age 60; FEV1 41%; BMI 24.5 kg/m², smokers 84%; paquets/ys 28. All the findings were compared in 34 normal age-, sex- and BMI-matched control subjects. BMD was measured in spine (L1-L4) and femoral necks (FN) in 15 men using DXA (Hologic)

**Results:** The level of BMD was significantly lower in 3rd group in comparison with control both in spine (0.992±0.156 vs. 1.252±0.119 g/cm2, p<0.01) and at femoral necks (0.824±0.136 vs. 0.986±0.065 g/cm2, p<0.01). Osteopenia and osteoporosis were diagnosed in 51% and 11% cases in the 2nd group; 30% and 66% in the 3d group respectively. Osteopenia was revealed in 50% patients in the 1st group.

**Conclusion:** We found the significant negative correlations between pack/ys and BMD of L1-L4 (r=0.55); with BMD of FN (r=0.38).

**Conclusions:** The significant decrease of BMD was found in the course of COPD progression.

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**P4605**

The relationship between inspiratory capacity and emphysematous changes assessed by CT in Vietnamese COPD patients
Hiroshi Wada, 1 Tho Nguyen Van, 2 Trung Le Thi Huyen, 3 Rie Kanda 1, Yasushi Ruyjin, 1 Masafumi Yamaguchi, 1 Tetsuya Oguma, 1 Taishi Nagao, 2 Emiko Ogawa, 1 Lan Le Thi Tuyet, 2 Yutasaka Nakano 1. 1Division of Respiratory Medicine, Department of Internal Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan; 2Faculties of Medicine, University of Medical and Pharmacy, Ho Chi Minh, Viet Nam; 3Health Administration Center, Shiga University of Medical Science, Otsu, Shiga, Japan

**Introduction:** It is known that low attenuation volume (LAV) assessed by computed tomography (CT) is related to the severity of chronic obstructive pulmonary disease (COPD). However, the relationship between distribution of emphysema assessed by LAV and inspiratory capacity is not clear.

**Objectives:** To investigate the relationship between IC and emphysematous changes in each lobe.

**Methods:** We recruited 76 Vietnamese COPD patients who underwent chest CT and respiratory function tests. We analyzed volumetric CT data and measured the fraction of low attenuation volume (LAV%) in each lobe. We then evaluated the relationship between LAV% in each lobe and inspiratory capacity.

**Results:** LAV% of the whole lung was significantly related to inspiratory capacity (r=0.278, p=0.021). LAV% in right lung and left lung were significantly related to inspiratory capacity (r=0.275, p=0.022, and r=0.2715, p=0.024, respectively). LAV% of the right upper lobe and middle lobe was not related to inspiratory capacity (p=0.075 and p=0.457, respectively). LAV% of the right lower lobe was significantly related to inspiratory capacity (r=0.354, p=0.003). LAV% of the left upper lobe was not related to inspiratory capacity (p=0.072). LAV% of the left lower lobe was significantly related to inspiratory capacity (r=0.371, p=0.002).

**Conclusions:** Inspiratory capacity is affected more strongly by the emphysematous changes in the lower lobes than in the upper lobes.
to get FMI, FFMI. The COPD pts were subdivided into groups: the 1st was made up of 14 men; 1 stage (GOLD); mean age 55 yrs; BMI 27 kg/m²; the 2nd - 43 pts; II stage; mean age 57; BMI 28 kg/m²; the 3rd - 20 pts; III stage; mean age 60 yrs; BMI 24.5 kg/m².

Results: Indices H, SD decrease, while E increases in COPD pts v. control and in process of severity growth of COPD. We have established the positive significant correlations of E with FMI (r=0.61), and negative one between SD and BMI (r=-0.7). The 1st group characterized by the positive significant correlations between E and FMI (r=0.69) and negative one between H and SD of extOAM and FMI (r=-0.42 and r=-0.52) in the 2nd group. The 3rd group characterized by the positive significant correlations between E and FMI (r=0.69) and negative one between H and SD of extOAM and FMI (r=-0.7 and r=0.75). The index E of intOAM correlated with FMI and FFMI (r=0.62 and r=0.63). Similar results were characteristic of other muscles.

Conclusions: The possible mechanism of the changes in COPD patients could be protein replacement with fat in muscles.

P4608 Distribution of CT-quantified emphysema: Association with lung function decline
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Background: Previous studies showed that subjects with similar extents of CT-quantified emphysema, but with different locations within the lung show different degrees of airflow obstruction.

Aim: To assess the association between CT-quantified emphysema distribution (upper/lower lobe) and lung function decline in heavy smokers participating in a lung cancer screening trial.

Methods: 587 participants underwent CT-scanning of the lungs and pulmonary function testing at baseline and after a median (interquartile range) follow-up of 2.9 (2.8-3.0) years. The lungs were automatically segmented based on anatomically defined lung lobes. Severity of emphysema was automatically quantified for anatomical lung lobe and was expressed as the 15th percentile technique (point below which 15% of the low attenuation areas voxels are distributed). Linear mixed models, correcting for age, height, BMI, packyears and smoking status, were used to assess the association of emphysema distribution and FEV1/FVC decline.

Results: Mean (SD) age was 60.2 (5.4) years, mean baseline FEV1/FVC was 71.6 (9.0%); overall mean Perc15 was 908.5 (20.9) HU. Participants with upper lobe predominant emphysema had a 1.71% (95% confidence interval 0.79 - 2.64) lower FEV1/FVC after follow-up compared to participants with lower predominant emphysema (p<0.001), independently of the total extent of emphysema.

Conclusion: Upper lobe predominant emphysema may be a different phenotype than lower lobe predominant emphysema.

P4609 Tracheo-bronchial collapsibility in different clinically determined COPD phenotypes
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Tracheo-bronchial collapsibility (TBC) has been detected at computed tomography (CT) in Chronic Obstructive Pulmonary Disease (COPD). TBC is considered a local response to inflammatory agents not closely related to the obstructive functional pattern and to lung attenuation values at CT. We hypothesize however that TBC could influence symptoms and daily performance in patients with COPD.

The purpose of our study was to investigate whether TBC is related to dyspnoea, exercise capacity and clinical phenotypes in patients with COPD.

Thirty-six patients (mean age 68±8, mean FEV1% 60±24) underwent clinical examination, lung function test, 6 minutes Walking Test and inspiratory-expiratory CT-TBC was measured by an automated software and correlated with MRC and Borg dyspnoea scales and with walked distance. Moreover we compared TBC in patients with predominant chronic bronchitis (CB) and predominant emphysema (E) phenotypes according to the rule available at www.clipcopd.com.

No significant relationship was found between TBC and MRC (r=-0.24, p=0.15), Borg score (r=-0.12, p=0.48),walked distance (r=0.17, p=0.33). TBC was significantly higher in patients with CB phenotype (p=0.02, Fig. 1). Patients with a predominant CB phenotype show a high level of TBC supporting the idea that the same inflammatory process could involve both trachea and bronchial tree. Dyspnoea and exercise capacity are global indexes of COPD that are not related to TBC.

P4610 Computed tomographic diagnosis of air trapping in non- or mildly obstructed smokers
Onno M. Mets 1, Pieter Zanen 1, Jan Willem Lammers 2, Ivana Isgum 3, Hester A. Gietsma 1, Bram van Ginneken 2, Pieter Zanen 1, Piem A. de Jong 1, 1Pulmonary, University Medical Center Utrecht, Utrecht, Netherlands; 2Pulmonology, University Medical Center Utrecht, Utrecht, Netherlands; 3Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands

To assess the association of emphysema distribution and FEV1/FVC-decline.

Models, correcting for age, height, BMI, packyears and smoking status, were used to assess the association of emphysema distribution and FEV1/FVC decline.

Results: Mean (SD) age was 60.2 (5.4) years, mean baseline FEV1/FVC was 71.6 (9.0%); overall mean Perc15 was 908.5 (20.9) HU. Participants with upper lobe predominant emphysema had a 1.71% (95% confidence interval 0.79 - 2.64) lower FEV1/FVC after follow-up compared to participants with lower predominant emphysema (p<0.001), independently of the total extent of emphysema.

Conclusion: Upper lobe predominant emphysema may be a different phenotype than lower lobe predominant emphysema.

P4611 Visual versus quantitative assessment of airways disease in COPDGene
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Background: Visual airway assessment may provide unique data not captured by automated methods; cut points for distinguishing “abnormal” from “normal” do not exist with quantitative CT (QCT) measures. We sought to understand the relationship between QCT and visual airway measures.

Methods: 198 COPDGene cohort scans (GOLD I-IV) were reviewed by pulmonary-monologists and radiologists (9-11 reviewers/scan) for presence of airway wall thickening (AWT). Logistic regression and area under the receiver operating curve (AUC) analyses determined the relationship between median AWT score and QCT measures including segmental and subsegmental wall area percent (WAP), wall thickness, lumen diameter and pi10 (standardized airway wall thickness at internal perimeter of 10 mm). Multivariate regression adjusted for age, gender, and smoking history was used to predict FEV1%, SGRQ and history of chronic bronchitis.

Results: Subsegmental WAP (AUC=0.72, p<0.001) and pi10 (AUC=0.75, p<0.001) best predicted the presence of visual AWT. A pi10 value of 3.78 (95th percentile normals/66th percentile COPD) provides 80% specificity and 55% sensitivity; a WAP value of 6 (>99th percentile normals/74th percentile COPD) provides 80%
specificity and 53% sensitivity. Subsegmental WAP predicted a similar degree of variability in FEV1% compared to AWT (r²=0.33 vs 0.32). Visual score better predicted chronic bronchitis symptoms (AUC 0.73 vs 0.66) and SGRQ score (r²=0.23 vs 0.16).

Conclusions: Expert panel visual airway score correlates best with subsegmental WAP and p<0.01 in the >90th percentile range for normals. Each method provides unique information; in particular, visual analysis scores appear to be more closely associated with clinical symptoms.

P4612
Analysis of activation process of dyspnea sensation in CNS in patients with COPD measured by fMRI
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2Advanced Medical Research Center, Iraku Medical University School of Medicine, Moriko, Japan

Introduction: Dyspnea is the cardinal symptom of COPD. Localization of dyspnea sensation in the brain has been studied by a small number of investigators. However little is known about transmission and activation of dyspnea sensation in CNS.

Objectives: We analyzed pathway and localization of dyspnea sensation in the brain of normal subjects and COPD patients using functional magnetic resonance imaging (fMRI).

Methods: Six normal subjects (M/F: 5/1, 35.7 ± 5.9 yr; mean ± SEM) and 4 COPD patients (M/F: 4/0, 68.5 ± 1.7 yr) were recruited. After informed consent, these subjects were requested to breathe through resistive loads ranging from 5 to 50 cm H2O/L/sec adjusted by the BORG 10 Scale. The subjects received Iminite of repetitive resistive-loaded breathing three times with lminute interval. During these process, brain activity was analyzed by 3 Tesla scanner (Signa Excite HD; GE Healthcare).

Results: Activation of bilateral sensory cortices was recorded among 6 normal subjects and COPD patients. In addition, VPM in bilateral thalami was also observed in all subjects when subjects breathed with the resistive load. There was no difference of the localization of activated portions during resistive-loaded activated in all subjects when subjects breathed with the resistive load. There was no difference of the localization of activated portions during resistive-loaded activated in all subjects when subjects breathed with the resistive load.

Conclusion: Activation of bilateral sensory cortices was dependent on the resistive load among normal subjects and COPD patients. The resistive loads on bilateral sensory cortices increased upon inspiration.

P4613
Anatomically derived regional measurement of lung function
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Existing methods for quantifying lung ventilation and perfusion SPECT scans provide measurements which are either global, based on division of the lung into non-anatomical regions or based on the application of a generic lung model of lung anatomy. The objective of this work is to develop a technique to use HRCT data to automatically define sub-lobar regions corresponding to anatomical lung segments and to align these with SPECT/CT data acquired separately from the same subject. This can be achieved by performing a non-rigid registration between the HRCT data, acquired at full inspiration, and the low-res CT data captured during tidal breathing. Once the transform required to bring these two data sets into alignment has been determined, it can be applied to the sub-lobar regions to map these to the low-res CT and hence to the SPECT data. This process of non-rigid registration is achieved using a free-form polynomial warp algorithm, which automatically determines the optimum elastic transform required to bring the HRCT and low-res CT data sets into alignment. HRCT scans are analysed using commercially available software to define the airway tree geometry, which is then used to seed a Voronoi space division algorithm to divide the lung into segments based on the branches of the airway tree. Early results have shown that it is possible to robustly divide the lung into the regions based on the segmental branches of the airway tree and good alignment between single 2D slices and the SPECT images has been obtained. The method will be extended to work in 3D and the results so far indicate that this will be a viable method to produce anatomically relevant measurements of lung function.
Results: 1757 patients were analysed: mean age 45.4 yrs; men 56.8%; current smoker 20.2%; mean time since diagnosis 16.8 yrs; 90% treated with ICS+LABA, 29% with antileukotrienes, 48% with antihistamines; 44% had severe exacerbation in past year; 33.3% had comorbidity which limited activities. According to GINA criteria (excluding lung function) 76.2% were not controlled. GPs reported limitation of activities in 44.4%. Whilst 87.4% of patients reported limitation of activity (mild, moderate or severe) at least one domain 75.2% daily, 80.5% physically and 50.3% work/school-activities.

Conclusion: Impact on asthma was frequent and underestimated among these treated patients. It deserves more attention when assessing asthma control.

P4616 Population segmentation to identify priority targets for identification and behaviour change interventions in COPD
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Background: In England 800,000 people are diagnosed with COPD. 2.7 million have the disease but are undiagnosed. Smoking is the dominant risk factor. Targeted identification of those at increased risk combined with effective behaviour change interventions could significantly reduce the disease burden.

Objectives: To identify and characterise those population groups in England at greatest risk of COPD in order to maximise the impact of targeted behaviour change interventions.

Methods: A social marketing methodology was employed. An England-wide audience segmentation based on life-stage, socio-economic and environmental factors was conducted to identify priority segments. Focus groups and interviews with informants in each segment provided a rich understanding of behaviours, attitudes and motivation.

Results: Three segments (children aged 7-12 and young men and women in routine/manual occupations) were identified as priority targets for prevention. Three further segments (mid-life men and women in routine/manual occupations and older routine/manual smokers) were identified as priority targets for identification of undiagnosed COPD. Two segments (Bangladeshi men and routine/manual parents who smoke) were identified as priority targets for both prevention and identification.

Conclusions: Targeting priority population segments will maximise the effectiveness of identification and behaviour change interventions in COPD and will ensure efficient use of healthcare resources. The results of this segmentation and insight work have informed development of the national strategy in England for the prevention and early identification of COPD.

P4617 Validity and reproducibility of a physical activity questionnaire for elderly
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Background: Physical activity is important for elderly to maintain their health and functional ability. It helps predict the course of chronic diseases. Many existing questionnaires have not been compared to activity monitors. We examined validity and reproducibility of the LASA Physical Activity Questionnaire (Lapaq) against an accelerometer in Dutch elderly (65+).

Methods: Participants were the accelerometer for two weeks and filled in Lapaq twice. We examined validity using correlation coefficients, histograms and modified Bland-Altman plots. We used logistic regression to assess how well Lapaq discriminates between persons who have sedentary lifestyle (30 minutes/day) and those who are physically active.

Results: 89 persons were included, 48% men, median age 73 and median BMI 25. 36%, 43%, and 22% had no, one, or two chronic diseases. As a reference, two full weeks contain 20160 minutes (336h). The total duration of activity in two weeks was 2439 (Lapaq T1), 1994 (Lapaq T2) and 2788 minutes (accelerometer). The difference between Lapaq T1 and accelerometer was 510 minutes (8.5 hours). The Pearson correlation coefficient was 0.34 (95% CI 0.13-0.51). The I.C.C. was 0.68 (95% CI 0.56-0.79). The area under the curve is 0.73 (95% CI 0.59 - 0.86).

Conclusions: Due to moderate reproducibility and low validity, Lapaq seems unsuitable for exact measurement of physical activity in elderly. If the more modest aim is to determine if a person’s activity level is above the recommendation level, Lapaq classifies around 73% correctly.

P4618 Urban-rural differences in health status among patients with chronic obstructive pulmonary disease (COPD)
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Background: While geographic variation in health care access and quality may affect health status of patients with chronic diseases little is known about the health status of patients with COPD.

Objectives: The purpose of this analysis was to examine urban-rural differences in health status among patients with COPD.

Methods: This was a cross-sectional analysis of baseline data from patients with COPD enrolled in a self-management clinical trial. Urban-rural residence was determined from zip code. Health status was measured using BODE index (BMI, obstructive impairment, dyspnea severity, exercise capacity), and generic (SF-12) and disease-specific (Chronic Respiratory Questionnaire [CRQ]) quality-of-life instruments. Independent sample t-tests and chi-square tests were used to examine statistical differences.

Results: To date, results from 82 patients are available with mean age of 69 years, 46% female, 51% rural residence, and 98.6% with health insurance. Rural residence was associated with greater impairment (mean [SD] BODE index=9.1 [8.9]) compared to urban residence (3.4 [1.8], p=0.0003). Moreover, 6-minute walk distance was clinically and significantly less among rural (325 m [104]) vs. urban (375 m [90]) (p=0.02) residence. A similar pattern was found for quality-of-life measures with a lower SF-12 physical summary score among rural (28.3 [9.6]) vs. urban (36.1 [10.0], p=0.0006) residence and clinically worse dyspnea (CRQ-dyspnea=4.1 [1.0]) vs. 4.8 [1.3], respectively, p=0.009.

Conclusion: In this population of patients with COPD rural residence was associated with poorer health status for all measures despite similar access to health care as measured by health insurance.

P4619 Screening of health status in patients with COPD in primary care is essential
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Background: Guidelines advice to measure health status (HS) in COPD patients. In secondary care (SC) this is more common than in primary care (PC). Problems in HS in PC might be underestimated resulting in inadequate treatment.

Aim: To investigate the proportion of COPD patients in PC with severe problems in HS.

Methods: 314 PC COPD patients were included. Eight sub-domains of HS were measured by the Nijmegen Clinical Screening Instrument (NCSI) covering Functional impairment, Symptoms and Quality of Life. Data from 303 SC COPD patients were available to compare the mean of the incidence and severity of problems in PC patients.

Results: Patients in PC did not differ on sex (59 vs 70% male) and age (mean 66 vs 67 years), but had less severe COPD compared to SC (Stage: 28 vs 16%; II: 59 vs 45%; III: 13 vs 32%; IV: 0 vs 8%). Lower proportions of patients with severe problems were found on the domain Functional impairment and the sub-domain Subjective symptoms in PC as compared to SC (Table 1). GOLD was not predictive for experienced problems in any of the sub-domains in PC.

Table 1. Percentages of patients with severe problems in primary care (PC) and secondary care (SC)

<table>
<thead>
<tr>
<th>PC (%)</th>
<th>SC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional impairment</td>
<td>31</td>
</tr>
<tr>
<td>Subjective symptoms</td>
<td>29</td>
</tr>
<tr>
<td>Dyspnea emotions</td>
<td>29</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>55</td>
</tr>
<tr>
<td>Health related QoL</td>
<td>23</td>
</tr>
<tr>
<td>Satisfaction relations</td>
<td>18</td>
</tr>
</tbody>
</table>

* p<0.01.

Conclusion: Severe problems in many sub-domains of HS were substantial in PC patients. In 5 of 8 sub-domains of HS similar percentages of COPD patients in PC and SC experience severe problems. This implies that screening for problems in HS is needed in PC to warrant patient tailored treatment.

P4620 Using community pharmacy to identify patients at risk of poor asthma control and potential contributory factors
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Aim: To describe a population identified by trained community pharmacists as being at risk for poor asthma outcomes, and to identify factors associated with poor asthma control.

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Methods: A cross-sectional study was conducted in 96 metropolitan and regional Australian pharmacies. Community pharmacists with specialised asthma training enrolled 570 patients aged ≥18 years with doctor-diagnosed asthma who were considered at risk based on suboptimal asthma control or lack of recent GP asthma review, and conducted a comprehensive asthma assessment. Assessment of asthma control was based on self-reported frequency of symptoms and activity limitation during the previous month. Asthma history, spirometry and inhaler technique were documented. Medication use was recorded from pharmacy records and self-report.

Results: 570 patients were recruited, of whom 437 (77%) had poor asthma control. 21% (n=120) had an action plan, 69% used combination inhaled corticosteroids (ICS)/long-acting β2-agonist (LABA) medications, and only 17.2% used their inhaler correctly. In terms of adherence, 90% had their ICS or LABA dispensed >6 times in the previous 6 months, which is inconsistent with regular use. A logistic regression model showed that patients who smoked, had incorrect inhaler technique or low adherence were more likely to have poor control.

Conclusions: Community pharmacists identified patients with asthma at risk of suboptimal control, and factors that contributed to this were identified. There is an opportunity within pharmacies to target poorly-controlled asthma and provide timely and tailored interventions.

P4621

Clinical determinants for oral steroids during COPD-exacerbations in primary care

P. van Velzen1, R.J.B. Loijmans 2, M. Amelink1, M. Stommel, G. ter Riet2, Anthony Davison1.

Background: Oral corticosteroids (OCS) are prescribed for most patients with moderate COPD, although not recommended in guidelines or product licences. The indication of systemic steroids during COPD-exacerbations is unclear. This study aimed to determine the proportion of mental disorders (anxiety and/or depression) in patients with COPD exacerbations that are dealt with by GPs in an out-of-hour setting.

Methods: All 18 patients who had called an ambulance because of an exacerbation of COPD in 17 days were included in the study. The ambulance service recorded the 12 relevant factors from the NICE guideline which should be considered when deciding to treat a patient at home. The aim of this study was to see what percentage of patients who had an exacerbation of COPD and call an ambulance meet the criteria for home treatment.

Methods: 1197 patients (14-90 years, median 37) of 107 Italian pharmacies were included in the study. The service recorded the 12 relevant factors from the NICE guideline which should be considered when deciding to treat a patient at home. The aim of this study was to see what percentage of patients who had an exacerbation of COPD and call an ambulance meet the criteria for home treatment.

Methods: The annualised median number of recorded exacerbations/year was 0.67 (range 0.6-6.7) overall and for those without concomitant asthma. 70% of those without asthma who did not have recorded exacerbations were prescribed ICS. Conclusion: ICS are prescribed for most patients with moderate COPD, although not recommended in guidelines or product licences. This prescribing cannot be explained by concomitant asthma or frequent exacerbations. Inappropriate use of ICS increases costs & puts patients at risk of side effects. GPs should audit their use of ICS in moderate COPD. P4624

Introduction: COPD is a chronic condition and healthcare policy in almost all countries is to try and deliver as much care for chronic diseases in the community and reduce the reliance and expense of hospital care. The National Clinical Guideline Centre (NICE) guidelines for COPD (2010) (www.nice.org.uk/guidance/CG101) give clear recommendations for factors to consider when deciding to treat a patient at home. The aim of this study was to see what percentage of patients who had an exacerbation of COPD and call an ambulance meet the criteria for home treatment.

Methods: All 1197 patients (14-90 years, median 37) of 107 Italian pharmacies were included in the study. The service recorded the 12 relevant factors from the NICE guideline which should be considered when deciding to treat a patient at home. The aim of this study was to see what percentage of patients who had an exacerbation of COPD and call an ambulance meet the criteria for home treatment.

Methods: The annualised median number of recorded exacerbations/year was 0.67 (range 0.6-6.7) overall and for those without concomitant asthma. 70% of those without asthma who did not have recorded exacerbations were prescribed ICS. Conclusion: ICS are prescribed for most patients with moderate COPD, although not recommended in guidelines or product licences. This prescribing cannot be explained by concomitant asthma or frequent exacerbations. Inappropriate use of ICS increases costs & puts patients at risk of side effects. GPs should audit their use of ICS in moderate COPD.

P4625

Prescribing patterns for allergic rhinitis in general practice setting: Adherence to ARIA guidelines

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Background: Allergic rhinitis (AR) and asthma are often co-morbidities. The correct management of AR should be ensured by the use of international ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines (GL).

Aim: To prospectively evaluate the adherence to GL of General Practitioners (GPs) for treating AR patients.

Methods: Analyses concern 1197 patients (14-90 years, median 37) of 107 Italian pharmacies.
P4626
General practitioners’ views about managing depression in patients with chronic obstructive pulmonary disease
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Introduction: Depression is common in patients with chronic obstructive pulmonary disease (COPD). COPD patients consult their general practitioners at least once or twice a year because of acute exacerbations. There is little data available on the management of depression in patients with COPD.

Aims: The study investigated general practitioners’ (GP’s) views about recognising and treating depression in patients with COPD.

Methods: We conducted a postal survey of 3,957 GPs in England about their views on recognising and treating depression in patients with COPD. The survey examined the GPs views using a likert scale (0 = strongly disagree, 2 = neither agree or disagree, 4 = strongly agree). The questions were prioritising treatment, value of screening for depression, difficulty of treating depression, best way of treating depression, depression exacerbates and interferes self-management of COPD.

Results: 3,957 general practitioners were mailed. Of these, 857 (22%) complete responses were received. Seventy-two percent of GPs agree screening for depression regularly, 9% disagree and neutral 19%. Prioritising treatment of COPD symptoms over depression21%, neutral 46% and 33% agree. Convincing COPD patients that depression needs treatment: disagree 27%, neutral 30% and agree 43%. Depression exacerbates COPD symptoms: disagree 9%, neutral 24% and agree 67%. Depression impairs self-management of COPD: disagree 4% and agree 96%.

Conclusions: Most GPs reported the importance of screening for depression regularly and depression impedes self-management of COPD. Over two-fifths of the GPs find it difficult to convince patients to offer treatment. Further studies are required.

P4627
Use of GOLD staging as a guide for treating COPD patients in primary care
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Introduction: The best strategies to reduce the costs derived from COPD are early diagnosis and adequate managing in initial phases. Our aim was to evaluate the adequacy of COPD treatment according to GOLD guidelines, in Primary Care (PC) patients.

Design & methods: Descriptive, transverse, multicentre study in 5 PC centers. Computerized clinical histories of patients with COPD diagnosis code were revised. We recorded spirometric data and current treatment of each patient. We evaluated spirometric confirmation of COPD, GOLD stage and adequacy of treatment according to GOLD.

Results: We analyzed 1220 patients (71.5% men), mean age 69.8 ± 13 years. 37.5% were never smokers. Rates of spirometry performance and spirometric confirmation of COPD were low (46.3% and 46% respectively). Adequacy of treatment to GOLD stage was 61.4%, and increased with severity of the disease (p<0.05). In GOLD 2, only 15.5% were using exclusively bronchodilators (BD). 40.4% were receiving inhaled steroids (IS) alone or in association to BD. 31.8% were taking “other” treatments (mucolytics, montelukast, oral steroids). In GOLD 3, 9.9% of patients were taking exclusively BD. 18.3% realized treatment with 2 BD associated to IS and 46.5% were using other treatments.

Conclusions: In many of the patients coded as COPD in PC, a spirometry lacks. The great proportion of never smokers raises doubts about correct codification. Prescription of IS and not inhaled treatments is too high in GOLD 2.
479. Cystic fibrosis: detection and monitoring of early lung disease

4655 Late-breaking abstract: VX-770, an investigational CFTR potentiator, in subjects with CF and the G551D mutation

Barry J. Plant1, Bonnie Ramsey2, Karl Yen3, Qunning Dong3, Sally Rodriguez2,3, Stuart Elborn4, Adult Cystic Fibrosis Centre, Cork University Hospitals, Cork, Ireland; 2Center for Clinical and Translational Research, Seattle Children’s Hospital, Seattle, WA, United States; 3Vertex, Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States; 4Adult CF Centre, Belfast City Hospital, Belfast, United Kingdom

Background: Restoring dysfunctional CFTR mediated ion transport is a potential treatment for CF. VX-770, a CFTR potentiator, is designed to increase CFTR ion transport activity.

Aims and objectives: This Phase 3 study evaluated the efficacy and safety of VX-770 in subjects with CF who have the G551D mutation on at least one CFTR allele.

Methods: A randomized, double-blind, placebo-controlled trial of subjects ≥12 years of age who received oral VX-770 150 mg q12h (n=83) or placebo (n=78) for up to 48 weeks.

Results: The mean absolute change from baseline through Week 24 in % predicted FEV1 (primary endpoint), improved by 10.4% in the VX-770 group, while the placebo group decreased by 0.2% (P<0.0001). This reflected a mean increase of 361 mL (P<0.0001) and a mean relative change from baseline of 16.9% of predicted FEV1 (P=0.001) in the VX-770 group compared to placebo. Improvement in FEV1 with VX-770 was evident at Day 15 and maintained through Week 48, at which time the VX-770 group showed an improvement of 10.1% (366 mL change) while the placebo group had a decrease of 0.4% (7 mL change). A 55% reduction in the risk of pulmonary exacerbations (P=0.0012) was observed through 48 weeks with VX-770 treatment. The reduction from baseline in sweat chloride, a biomarker of CFTR activity, was −48.1 mmol/L through Week 48 in the VX-770 group compared to placebo (P<0.0001). The safety profile of VX-770 was comparable to placebo.

Conclusions: VX-770 demonstrated a clinically relevant and statistically significant improvement in pulmonary function and reduction in pulmonary exacerbations and sweat chloride up to 48 weeks of treatment. The safety profile was similar to placebo.

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4656 Improvement in lung function during the 1st year of life in infants diagnosed with CF through newborn screening (NBS)

Lena Thia1,2, Ah-Fong Hoo1,2,5, Thanh-Diem Nguyen1, Deeba Ahmed1, Barry J. Plant1, Bonnie Ramsey2, Karl Yen3, Qunning Dong3, Stephen Stick4, on behalf of AREST CF.

Methods: Multiple breath washout and raised volume techniques were performed in CF infants from 6 tertiary CF centres in London, UK and prospectively recruited HC.

Results: 35 CF and 18 HC infants have completed paired measurements at 3 months (T1) and 1 year (T2). Significant improvements in the CF group were seen in anthropometry, LCI, FEV0.5 and FEF25–75 z-scores by T2, with no significant differences from HC at this stage, except for a slightly elevated LCI.

Hypothesis: These reductions in LF persist to 1 year of age.

Objective: To compare the presence and extent of CF structural lung disease detected on volumetric inspiratory and expiratory scans in young children.

Methods: 38 children with CF age 1-5 years underwent inspiratory and expiratory volumetric chest CT. De-identified scans were assessed in random order by 2 observers using the Brody II score. Intraclass correlation coefficients (ICC) and Bland-Altman plots using mean scores determined agreement between expiratory and inspiratory scans.

Results: There was substantial agreement between mean Brody II component scores from inspiratory and expiratory scans (ICC range 0.637 to 0.866). For Bx, the ICC was 0.864, however, there was a systematic bias evident on Bland-Altman plot as shown, with consistently higher scores on inspiration. Further, analysis of binary outcomes (presence/absence of Bx) indicated that Bx was not demonstrated.

References:
on the expiratory scan in 40% of subjects when demonstrated on the inspiratory scan.

Conclusions: In early CF Bx, the presence and extent of Bx is underestimated with expiratory scans alone compared with inspiratory scans.

4659
Magnetic resonance imaging (MRI) as a non-invasive, radiation-free imaging modality to study the onset and progression of lung disease in infants and young children with cystic fibrosis
Monika Eichinger1, Eva Fritzsche2, Annette Kopp-Schneider2, Migle Simcinauskaitė1, Daiva-Elzīta Optaze1, Marcus Maß2, Michael Puderbach1,2,4. 1Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; 2Pediatric Pulmonology and Cystic Fibrosis Center, University Hospital Heidelberg, Germany; 3Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany; 4Diagnostic and Interventional Radiology, Thoraxklinik, Heidelberg, Germany; 5Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

Little is known about the onset and spontaneous progression and routine lung function testing is not available for monitoring of early CF lung disease. The aim of the present study was to validate pulmonary MRI to study the onset and progression of lung disease in infants and young children with CF. In 34 CF patients (age: 2.5±0.4; 17f, 17m) MRI (1.5T) was performed in free breathing. For morphological imaging a T2w-(HASTE PACE) and a T1w T1-TSE sequences pre and post contrast media in coronal and transversal orientation were used. Functional imaging was performed using a 3D-FLASH sequence with a temporal resolution of 1.5s after iv injection of Gadolinium-DTPA. Two independent radiologists analyzed the images with a dedicated MRI score (range 0-72). Morphological and functional abnormalities in the CF lung were detected by MRI in the first year of life (CF score 6.3±1.1; n=6) and the score increased significantly to 16.2±1.7 (p < 0.05; n=5) at the age of 4 years. Perfusion defects were reversible in follow up scans in a substantial number of patients. Further, MRI scores were reduced after antibiotic therapy for pulmonary exacerbations (pre treatment: 20.2±7.7 vs post treatment: 13.0±4.9; p<0.05).

Our study indicates that MRI of the lung is sensitive to detect abnormal morphology, function and response to therapy in early CF lung disease. These results suggest that MRI may be suitable for non-invasive diagnostic monitoring of disease severity and may serve as a novel endpoint for clinical trials in early CF lung disease. Supported by Mukoviszidose e.V.

4660
What is the significance of aspergillus fumigatus in BAL in children with cystic fibrosis
Rebecca Thursfield1, Andrew Bush1, Alex Adams1, Andrew G. Nicholson2, Katy Holden1. 1Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom; 2Department of Histopathology, Royal Brompton Hospital, London, United Kingdom

Background: Aspergillus fumigatus (AF) is frequently found in the airways of children with cystic fibrosis (CF) and recent evidence suggests this may be clinically important. (Chest 2006;130:222, Ped Pulm 2007;42:785)

Aims: In this retrospective study, we hypothesised that children with CF who have AF seen on direct staining of bronchoalveolar lavage (BAL) will have a worse clinical state than both those who only culture AF (positive controls) and those with no isolation (negative controls). Primary outcome was FEV1; secondary outcomes included BMI, IgE, IV antibiotics, steroids and antifungals.

Results: In the year prior to bronchoscopy (FBO), the groups were similar in terms of weight centile, IV antibiotics received and FEV1. One year post FOB, the groups with AF in their BAL, on cytology or microscopy, had a lower FEV1 despite receiving more IV antibiotics and more antifungal therapy.

Conclusions: The results add to the growing evidence that AF in the airways of children with CF is associated with a worse clinical state, whether identified on direct smear or culture.

4661
Newborn screening for cystic fibrosis improves lung function and growth at time of transfer to adult care
Nicole Dijk, Karen McKay, Federica Barzi, Dominic Fitzgerald. Respiratory Medicine, The Children’s Hospital at Westmead, Sydney, New South Wales, Australia

Introduction: Newborn screening (NBS) for Cystic Fibrosis (CF) is associated with improved early nutritional outcomes and improved spirometry in children. Aim: To determine whether the early diagnosis and treatment of CF with NBS in NSW in 1981 led to better clinical status and survival at transfer to adult care.

Methods: Retrospective observational study comprising 2 cohorts: diagnosed symptomatically in the 3 years before newborn screening was introduced (“non-screened”) and diagnosed in the first 3 years of NBS (“screened”). Patients were followed up until transfer to adult care, before age 19 years. ANOVA was used for clinical outcomes & survival was compared using a Cox proportional hazard model.

Results: Compared with non-screened patients (n=55), screened patients (n=56) were less likely to have pseud. aeruginosa in sputum at diagnosis (p=0.001), older when they acquired pseudomonas (p=0.001) & had better lung function when transferred to adult care: higher FEV1%, (mean difference = 17.2%; P = 0.012), FVC% (16.7%; P = 0.021) and a non-significantly higher BMI (0.95 Kgm²; P = 0.143). There was a non-significant 41% mortality risk reduction in screened patients as compared to non-screened patients (Hazard Ratio (95% CI): 0.59 (0.24-1.43); p =0.25). Each 1% increase in FEV1% was associated with a 3% decrease in risk of death (p=0.002) and each 1 unit BMI increase was associated with an 46% decrease in risk of death (p<0.001).

Conclusion: NBS for CF leads to better lung function and nutritional state at time of transfer to adult care in screened patients. Both outcome measurements are good predictors for long term survival.

482. How to improve lung cancer care

4670
Time to diagnostic procedures and treatment in outpatients diagnosed of lung cancer (LC) included in our rapid diagnosis protocol (RDP)
M. Isabel Andrade, Tamara Gutierrez, Amaia Irizoy, Jose Antonio Cascante, Pilar Cebollero, V. Manuel Eguia, J. Javier Huerto. Pneumology B Department, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain

Aim: To determine the time to diagnose procedures and treatment in outpatients diagnosed of LC in Navarra (Spain) included in a RDP.

Method: Retrospective analysis of outpatients diagnosed of LC in our RDP from January 2006 to October 2010. The reference date was the day they were sent to our service. We analyzed time to CT, to bronchoscopy, to endobronchial ultrasound transbronchial needle aspiration (KT-EBUS), to transparietal fine needle aspiration (TFNA) and to Positron emission Tomography (PET), time to treatment and the hospitalization average.

Results: 70 patients were diagnosed of LC in our RDP; 80% were men, the mean age was 63.9; 68.5% were remitted from primary care (PC). The mean time to
the last diagnostic procedure was 22.5 days from PC and 16.4 from first visit in our RDP (RDPfs). The table reflects time from PC* or other remission service or RDPfs to each procedure.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC*—RDPfs</td>
<td>70</td>
</tr>
<tr>
<td>RDPfs—CT</td>
<td>70</td>
</tr>
<tr>
<td>RDPfs—Bronch.</td>
<td>51</td>
</tr>
<tr>
<td>RDPfs—TFNA</td>
<td>20</td>
</tr>
<tr>
<td>RDPfs—TFNA</td>
<td>4</td>
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<tr>
<td>RDPfs—TFNA</td>
<td>1</td>
</tr>
<tr>
<td>RDPfs—PET</td>
<td>33</td>
</tr>
<tr>
<td>RDPfs—EBUS</td>
<td>9</td>
</tr>
</tbody>
</table>

We use PET since 2006 and EBUS since October 2008. 75% of patients didn’t need hospitalization. The mean days, when needed, was 3.1 (I–3). Patients required surgical treatment in 22.8%, oncologic in 68.5% and Palliative Care as first choice in 8.7%. The time from PC* to treatment was 37.4 days (5-103) and from RDPfs to treatment was 31.4days (0-90).

Conclusions: With our RDP we have achieved a lower time delay to diagnosis and treatment (no difference between kind of treatment) of LC comparing with most of the existing recommendations.

We haven’t need hospitalization in most cases and the mean of days was low.

4671 Self reporting of symptoms and delays in patients presenting to a rapid access lung cancer clinic (RALLC)
Mateen Uzbeck, Colm Geraghy, Eleanor Dunican, Seamus Linnane, Ross Morgan. Respiratory Medicine, Beaumont Hospital, Dublin, Ireland

Introduction: The RALLC at our hospital is aimed at expediting the diagnosis of suspected thoracic malignancies.

Methods: A self-reported questionnaire to consecutive patients on their first visit. Patient’s perception of why they were attending, symptoms, duration before seeking medical attention, time to referral and risks for lung cancer recorded.

Results: 154 patients, 81 male, 73 female, mean age 63 years (21-86). GP’s made most referrals 87% and 68% perceived abnormal radiology as reason for attendance. Majority were symptomatic 86.6% with 57% reporting ≥3 symptoms. Cough was most common presenting symptom 61%, fatigue 52%, dyspnoea 45%, chest infection 45%, chest pain 40%, weight loss 32% and haemoptysis 25%. Haemoptysis had the least delay in presenting to a health care provider (mean 30 days, range 2-120) whereas for cough, dyspnoea and chest pain mean delay was 4.5 months. Average delay in seeking medical attention and referral to RALLC was 14 weeks. 72% were current or ex-smokers and 21% reported at least one first 3 symptoms.

Conclusions: Significant delays exist between symptom onset and presentation to a health care provider and depends on symptom type. The bulk of the delay was before patients sought medical attention but there was still a sizeable delay between presentation and referral to RALLC. One in 5 patients had a first degree relative with lung cancer indicating that this may have been a factor in the decision to refer. Our study highlights the need for increased public awareness regarding the presenting symptoms of lung cancer and there exists the opportunity to reduce delays in diagnosis resulting in better outcomes.

4672 Managing patient pathways to achieve lung cancer waiting time targets:
Hugh Ig 1, Tarik Amer, Michael Dangorf, Alan Zamir, Darryl Gibbings-Isaac, Ranjeet Kochhar, Timothy Heymann 1. General Medicine, Guy’s and St Thomas’ Trust, London, United Kingdom; 2Health Management, Imperial College Business School, London, United Kingdom

Background: England’s NHS introduced a 62-day target, from referral to treatment, to make lung cancer patient pathways more efficient. This study aims to understand pathway delays that lead to breaches of the target when patients need care in both secondary and tertiary setting so more than one institution is involved.

Methods: Mixed method cross case analysis. Qualitative methods include pathway mapping and semi-structured interviews. Quantitative analysis of patient pathway times from cancer services records.

Setting: Two tertiary referral hospitals in London

Participants: Database records of 53 patients were analysed. 19 sets of patient notes were used for pathway mapping. 17 doctors, 4 nurses, 8 managers and administrators were interviewed.

Results: The majority of the patient pathway (68.4%) is spent in secondary centres. There is more variability in the processes of secondary centres but tertiary centres do not have perfect processes either. Three themes emerged from discussions: information flows, pathway performance and the role of the multidisciplinary approach.

Conclusions: The actions of secondary centres have a greater influence on whether a patient breaches the 62-day target, compared to tertiary centres. Nevertheless variability exists in both, with potential for improvement.

4673 Lung cancer multi-disciplinary team (MDT) decisions audit
Brendan Mallaia-Milanes, Jenny Graves, Jeffrey Mercham-Jones, Sulyn Leong, Ian Mortmone, Steve O’Higgins. Respiratory Medicine, Hereford County Hospital, Hereford, United Kingdom; 3Thoracic Medicine Department, Gloucester Royal Hospital, Gloucester, United Kingdom; 4Respiratory Medicine, Cheltenham General Hospital, Cheltenham, United Kingdom; 5Respiratory Medicine, Worcester Royal Hospital, Worcester, United Kingdom

Background: Lung cancer resection and survival rates in the UK vary; the reasons for this are unclear.

Aims: To compare lung cancer MDT decision outcomes in 4 hospitals in one cancer network.

Methods: Each lung cancer MDT randomly selected 5 of their MDT cases and submitted them to the other MDTs for assessment. MDT decision outcomes for each case, including each MDT’s own previously discussed MDT cases were collated. Mean percentage agreement of MDT outcomes was calculated for TNM staging and referrals for PET scan, curative surgery, radical radiotherapy and palliative chemotherapy.

Results: 3 hospital MDTs discussed 15 cases as well as having previously discussed their own 5 cases. 1 hospital submitted their 5 previously discussed cases but failed to discuss the other cases submitted to them. There were 17 non-small cell lung cancer cases, 2 indeterminate cases and 1 small cell lung cancer case. The number of cases referred for curative surgery varied between 6 to 7 cases per MDT. Percentage agreement was 83% for T staging, 91% for N staging, 98% for M Staging, 87% for referral for PET scan, 98% for curative surgery referral, 95% for radical radiotherapy referral and 93% for palliative chemotherapy referral.

Discussion: There was good agreement for staging and very high agreement for treatment referral. In this pilot study the high agreement for potentially curative treatment does not support the view that some MDTs are not referring patients for potentially curative treatment. As numbers are small we propose this issue be addressed by a national web-based quality assurance programme where each MDT assesses and reports sample cases each month and is given formative feedback.

4674 Histological typing of lung cancer in biotopically obtained specimens under the aspect of therapeutical approaches – A multi-center study
Annette Fisseler-Eckhoff 1, Raca Zinszy 1, Pieran Laenger 1, Phillip Schnabel 1, Iver Petersen 2, Klaus Junker 5. 1Dr. Horst-Schmidt Kliniken, Institute of Pathology and Cytology, Wiesbaden, Germany; 2Medizinische Hochschule Hannover, Institute of Pathology, Hannover, Germany; 3Universitaetsklinikum Heidelberg, Institute of Pathology, Heidelberg, Germany; 4Universitaetsklinikum Essen, Institute of Pathology, Jena, Germany; 5Klinikum Bremen Mitte, Institute of Pathology, Bremen, Germany

The insufficiency of classifying lung cancer as SCLC or NSCLC clinical arose with the approval of the antifolate pemetrexed, which has a lower antitumourous effect in Squamous Cell Carcinoma. Often only biopsy specimens are available to exclude a squamous differentiation before chemotherapy decision.

The restrictive nature of subtyping lung cancer in biopsies demanded a skilled and experienced pathologist. This interlabatory comparison should discover the accuracy of subtyping of lung cancer biopsies evaluated in 5 different pathological institutes in Germany. Is it possible to improve the accuracy histological typing by additional immunohistochemistry (IHC) panel?

60 biopsy specimens with Hematoxylin-eosin (HE) stain and immunohistochemical stained slides of at least Ck7, Ck5/6, p63, TTF1 were assembled and analysed by the pathologists. An estimation of predominantly-non-squamous yes/no and the histological subtype was done after examination the HE slide and again after the examination of the IHC. These two results were compared.

All 60 cases were analysed by all 5 participants. In average the agreement of
483. The impact of the organisation of care on costs: the role of the physician in home care

487 An evaluation of the safety, efficacy and cost-effectiveness for patients with acute respiratory illness, of a community-based intravenous medication service: The first 26 months
R.A. Khan1, J.P. Cullen2, S. Zaidi3, 1Short Term Acute Care Unit (SACU), Adelaide and Meath Hospital, Tallaght, Dublin, Ireland

Background: Patients with acute respiratory illnesses such as acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and pneumonia occupy significant proportion of acute hospital beds. There is therefore an increasing focus on intermediate care initiatives to facilitate early supported discharge (ESD) and admission avoidance (AA) in such patients. Since 10.11.08, our hospital in partnership with Community Intervention Team (C.I.T) provided service for administration of intravenous (IV) medications, facilitating ESD/AA.

Aim: To evaluate the AMNCH/C.I.T. IV service, in terms of safety, readmission rates, adverse events, bed-days saved, patient satisfaction and cost-effectiveness.

Results: Up to 31.11.1, of 285 patients referred to this service, 32% had a primary diagnosis of acute respiratory illness. 44 patients were male, 48 female. Mean age was 58.5 years (range 18-95). ESD and AA was facilitated in 67% and 33% respectively. Respiratory diagnoses were: pneumonia (n = 63), AECOPD (n = 7), exacerbation of asthma (n = 4), exacerbation of bronchiectasis (n = 5) and non-pneumonic respiratory infection (n = 13). IV treatment saved a minimum of 486 bed-days. Average length-of-stay in the service was 5.3 days. Readmission rate was 3.2%. No adverse incidents were reported. Patient satisfaction was 100%. We estimate that home treatment of these patients saved €457,300 for AMNCH compared to equivalent treatment in hospital.

Conclusion: We conclude that the service continues to be a safe, effective, inexpen-

4877 Potential economic savings of administration of home intravenous antibiotic therapy to patients with acute respiratory infections in Ireland
Melissa McDonnell1, 2Maurice Power2, Robert Rutherford1, J.J. Gilmartin1, J.J. Gilmartin. 1Respiratory Medicine, University Hospitals Galway, Galway, Ireland; 2Department of Finance, University Hospital Galway, Galway, Ireland

Introduction: Acute respiratory infections (ARI) account for a significant propor-
tion of prolonged hospital stays. Intermediate care initiatives supporting home intravenous antibiotics (HIV A) aim to facilitate early discharge and avoid unnec-

sary admissions. Numerous studies have demonstrated the efficacy of HIV A for acute infections. International studies have shown increased patient satisfaction, improved quality of life, fewer investigations, less cross-infections, decreased social disruptions and increased cost-effectiveness.

Objective: The purpose of this study was to analyse the potential cost-effectiveness of HIV A in patients with ARI in Ireland.

Methods: Using the Health Service Executive (HSE) Casemix and assuming a 60% uptake of ARI patients satisfying HIVA criteria with a length of stay (LOS) of 1-3 days, cost-estimates relating to cost/bed and LOS were used to calculate cost/day savings if HIV A is introduced.

Results: The approx. annual admission rate for ARI conditions such as pneumonia, COPD, asthma, CF and bronchiectasis is 26,700 patients/yr with an average cost per admission of €70,600. Based on an average LOS of 9.2 days at a cost/bed day of €1,920, the cost/ARI admission is €17,664. This equals to €473m. An LOS of 1-3 days would result in cost-estimates of €51.4-154.2m, a gross difference of €318.8m. Accounting for expenses such as capacity, staff, training, equipment, travel and others, we estimate bed-day savings of €200-220m/yr.

Conclusion: HIVA administration is a safe, cost-effective alternative in suitable patients with ARI, potentially providing significant savings to the health service in Ireland.

4879 A prospective re-audit of admissions and discharge delays occurring in patients admitted to a district general hospital’s respiratory ward in the United Kingdom
Christopher Chadwick, Diane Murray, Rahul Sarkar, Ana de Ramon Casado.
Respiratory Ward, Warrington and Halton NHS Foundation Trust, Warrington, Cheshire, United Kingdom

Introduction: The National Confidential Enquiry into Patient Outcome and Death recommends that following initial assessment and treatment, patients should be transferred to a ward which is appropriate for their clinical condition.

Objective: To assess delays prior to discharge for patients (respiratory vs non-

respiratory) whom are medically fit for discharge, following a reduction in respir-

atory beds from 62 to 46 as recommended by Sarkar et al 2010.

Methods: A prospective 2-week audit was conducted on respiratory wards and in-

A summary table comparing the current re-audit to the previous initial audit

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<td>Mean age of patients(yr)</td>
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4680
The attitude of physicians for asthma treatment and results in the inhaler market between 2004-2009 in Turkey
Sedat Altim1, H. Volkan Kara2. 1Department of Chest Diseases, Yeditepe Education Hospital for Chest Diseases and Thoracic Surgery, Istanbul, Turkey; 2Department of Thoracic Surgery, Gumushane State Hospital, Gumushane, Turkey
We evaluated the effects Turkey Conversion Programme in Health in 2004 on drug market and physicians attitude for asthma treatment. We analyzed the data from IMS the programme following the drug market and the data from the Social Security Institution (SSI) for comparative studies. In 2004 SSI paid nearly 4.0 billion Euro for drugs which increased to 8.5 billion (190%) in 2009. Inhaled corticosteroids were the most used drugs (52.7%). The cost of inhaler asthma drugs was 88.9 million and increased to 280.6 million (3.16 fold). Drug prescribed was 6.037.122 and increased to 20.848.085 boxes (3.45 fold).In the market of subgroup for inhaler dust asthma drugs distribution was: the rescue drugs 31.5%, combined drugs 17.7%, nebulisers 10.5%. The rates in 2009 were 20.2%, 29.6% and 18% respectively. Economically distribution was: 48.4% for combined drugs, 6.3% for nebuliser and 6.3% for rescue drugs. Rates for 2009 were 58.4%, 9.2% and 4.1%. The number of rescue drugs increased from 1.901.938 boxes to 4.220.664 (2.22 fold). The financial increase was 4.62 fold from 5.570.177 to 25.739.326. The number for nebuliser was 631.184 and increased to 3.762.806 (5.96 fold) the cost for them was 5.570.177 increased to 25.739.326 (4.62 fold).The combined drug subgroup the number of prescriptions increased to 1.066.486 increased to 6.178.315 (5.79 fold).The cost was 43.006.559 and increased to 163.814.343. There has been an increase in the costs for inhaler drugs used for asthma treatment. Our analyses showed that this increase mostly caused by increase in the number of prescribed combined drugs. This increase we believe decreased the need for rescue drugs but had no effect on the nebulisers that has been used increased.

4681
Stepping up the controller medication in asthma patients: Impact of various treatment options on costs
Mohsen Sadatsafavi1, Pierrick Bedouch1, Mark FitzGerald1, Carlo Narra1, Larry Lund2, 1Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; 2Department of Medicine, University of British Columbia, Vancouver, BC, Canada
Introduction: To compare asthma-related costs among adults who step-up their controller medication.
Methods: A population-based study was conducted using the administrative health data from the Ministry of Health, Canada (1997 to 2007). Hospitalization, physician visits, and prescription records were used to identify asthma patients (age 14-65) and calculate direct costs. Four cohorts were constructed as those who: increased the dose of inhaled corticosteroids (ICS group), switched to ICS/long-acting beta-agonist (LABA) in a single formulation (ICS/LABA group), added LABA in separate formulations (ICS+LABA group), or added leukotriene receptor antagonist (ICSLRA group). The outcome was the direct cost of asthma (2008 CAD) in the year after the step-up, adjusted for multiple demographic, resource use, and comorbidity variables from the previous year.
Results: 52,640 patients (average age 42.3, 60.3% female) were included (7,115 ICS+, 9,457 ICS/LABA, 4,086 ICS+LABA, and 1,982 ICS/LRA). The average cost of asthma for the year after the index date for the ICS+ group was $350. Compared to ICS+, all other groups had significantly positive incremental costs: $358.0 for ICS/LABA, $350.4 for ICS+LABA, and $554.6 for ICS/LRA (all P-values<0.01). Higher age, higher resource use, and higher cumulative dose of rescue medication in the year prior to the step-up date were predictors of higher costs after the step-up date (all P<0.01).
Conclusions: Based on relatively large sample and adjusted for several potential confounders, increasing ICS dose as a step-up approach was associated with the lower costs compared to addition of a second class of controller medication.

4682
The cost and diagnostic efficacy of microbiological evaluation of exudative pleural effusion
Serpi Tegül, Semra Bilacergolu, Hatrice Kuman, Ali Kadri Cirak, Sveket Ozkaya. Department of Pulmonary Diseases, Dr. Suat Seren Education and Research Hospital for Chest Diseases and Thoracic Surgery Hospital, Izmit, Turkey
Purpose: To evaluate the cost and diagnostic efficacy of microbiological studies of pleural fluids.
Method: Hospitalized patients with exudative pleural effusion were prospectively evaluated. The fluid samples were examined for Gram stain, acid-fast bacilli smear together with specific bacterial, fungal and mycobacterial cultures.
Results: Bacteriologic and EZN stains of the pleural fluids were negative in 89 cases included whereas fluid cultures were positive in 9 (10.1%) cases [3 (12.5%) of the 24 with tuberculous pleurisy and 6 (28.5%) of the 21 with empyema or other parapneumonic pleural effusion]. The cultures of the malignant, nonspecific and paracarcinomatous fluids were negative. In cases with empyema or other parapneumonic pleural effusion and tuberculous pleurisy, no significant difference was determined between culture-positive and culture-negative cases regarding age, gender, fever or fluid LDH and glucose levels; positive cultures were more frequent in the presence of fluid purulence (55.6% versus 8.3%, p=0.046). In 5 (83.3%) of the 6 culture-positive and in 6 (40%) of the 15 culture-negative cases with empyema or other parapneumonic effusion, change in antibiotic treatment was necessary. The costs of the microbiological studies was $39.4 Euro for each case and 1735 Euro and 1419 Euro for cases with noninfectious and infectious fluids, respectively.
Conclusion: Diagnostic yield of the routine microbiological studies of pleural fluids was determined low. It was concluded that requesting microbiological studies of pleural fluids in cases strongly considered to have infection on clinical basis or in cases with purulent fluid would be more beneficial regarding diagnostic yield and cost.

4683
Bitter taste receptor agonists as a novel class of bronchodilators in guinea-pig airways
Ville Pulkkinen, Jesper Säfholm, Martijn Manson, Mikael Adner, Sven-Erik Dahlén. Department of Experimental Asthma and Allergy Research, The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
Rationale: Despande et al. (Nat Med 2010) reported that several bitter taste receptor agonists (TAS2K) agonists evoked relaxation of mice and human airways. We examined the effects of three prototype agonists in segments of guinea pig trachea (GPT).
Methods: GPT was pre-contracted with 0.1 μM carbachol in both absence and presence of 3 μM indomethacin or prostaglandin antagonists. The segments were either exposed to denatonium, chloroquine or saccharin, or kept untreated. Expression of TAS2Rs in guinea pig tracheal epithelium and smooth muscle was measured with real-time PCR.
Results: Denatonium and chloroquine induced concentration-dependent relaxations whereas saccharin had no effect. In consistency with these findings, there was expression of TAS2R4 and TAS2R10 in GPT. There has been an increase in the costs from 2004 to 2009 in Turkey.

4684
Prostacyclin modifies VEGF synthesis in fibroblasts from healthy and COPD patients
Anna-Karin Larsson1, Oskar Hallgren 1,2, Mark FitzGerald1, Carlo Narra1, Larry Lund2. 1Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
Background: Involvement of vascular remodelling in the lung is a characteristic sign in chronic obstructive lung disease (COPD). The vascular mediator prostacyclin may regulate fibroblast activity. The objective was to study the effect of prostacyclin on synthesis of vascular endothelial growth factor (VEGF) and interaction with transforming growth factor (TGF) B in distal lung fibroblasts from patients with COPD and control subjects.
Methods: Prostacyclin modifies VEGF synthesis in fibroblasts from healthy and COPD patients

484. Translational models of airway disease

484.1
Translational models of airway disease

484.2
Translational models of airway disease

852s
Results: Iloprost enhanced VEGF synthesis in both fibroblasts from control subjects (p<0.05) and 6-1-fold from patients with COPD (p<0.01). However, iloprost showed no effect on VEGF synthesis after TGF-B1 stimulation, whereas indomethacin reduced VEGF production in fibroblasts from patients with COPD (p<0.05) but not in control subjects. 

Conclusions: Iloprost enhanced VEGF synthesis in fibroblasts from both healthy and patients with COPD. Though, iloprost had no effect on VEGF after TGF-B1 stimulation. These data indicate that also other proangiogenic mediators are involved in the regulation of VEGF in fibroblasts from COPD patients.

4685
Capsazepine inhibits NF-κB subunits in dsRNA-exposed human bronchial epithelial cells from asthmatic and COPD donors
Imre Némethivitvök Persson1, Angelica Brandelitana2, Leif Bjørmer2, Jenny Calvén1, Yuliana Yudina1, Lena Uller1
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Background: Novel drugs are needed to treat vial-induced exacerbations of asthma and COPD. We have shown that capsazepine (CPZ) inhibits vial-induced cytokine production (including thymic stromal lymphopoietin, TSLP) in human bronchial epithelial cells (HBEC) more effectively than steroids. 

Objective: Investigate NF-κB mechanisms potentially involved in actions of CPZ in HBECs from patients with asthma and COPD. 

Methods: Primary HBEC were obtained by fibre optic bronchoscopy from individuals with asthma (n=6) and COPD (n=3), then grown in 12-well plates and stimulated with viral surrogate dsRNA (10 μg/ml) to induce pro-inflammatory cytokine (TSLP, TNF-α, IL-8, IFN-β) mRNA expression (RT-qPCR) and production (ELISA). CPZ (3-30 μM) was added 1 h prior to dsRNA. NF-κB-signaling was studied (western blot) using specific antibodies for NF-κB subunits p65, p105 and IκBα. In vivo synthesis of IκBα and NF-κB was studied by RT-qPCR.

Results: dsRNA induced marked expression and release of TSLP, TNF-α, IL-8, and IFN-β (p<0.001). These effects were dose-dependently reduced (p<0.05-0.001) by CPZ. Both NF-κB and IκBα were inhibited by CPZ. Inhibition of NF-κB prevented degradation of IκBα and NF-κB signaling.

Conclusion: CPZ effectively reduced dsRNA-induced cytokine overproduction in HBECs from asthmatic and COPD donors. CPZ inhibited dsRNA-induced IκBα degradation preventing dissociation and translocation of p65 to the nuclear fraction. CPZ may stabilize IκBα thus inhibiting NF-κB-dependent cytokine production.

4686
Bradykinin-induced contractions in guinea pig trachea after incubation and culture
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Background: Inflammatory conditions can alter responsiveness to the endogenous peptide bradykinin (BK). Methods: The contractile response to BK was determined in organ tissue baths. 

Methods: Study the regulation of BK responses by culture procedures. Our data suggest that TIP peptides with charge distribution enhancing amiloride-sensitive current than the latter: the most active peptide had an EC50 of 19.9 nM. Compared to TNF-alpha (EC50 8.2 nM) and the original human TIP peptide (EC50 28 nM) for their ability to enhance sodium transport was observed at 120 nM. Compared to TNF-alpha (EC50 8.2 nM) and the original human TIP peptide (EC50 54.3 nM), several of the newly-designed peptides were more effective at enhancing amiloride-sensitive current than the latter: the most active peptide had an EC50 of 19.9 nM. Our data suggest that TIP peptides with charge distribution and interatomic distances most closely resembling the 3D structure of the native lectin-like domain of TNF-alpha, are those with greater ability to enhance activation of sodium current through ENaC. No standard therapy exists for pulmonary oedema, thus these TIP peptides represent promising therapeutic agents for activating sodium uptake from the alveolar fluid through ENaC and improving clinical outcome in this condition.

4687
Protective effect of a protein epitope mimetic (PEM) CCR10 antagonist, POL7085, in an allergic model of asthma
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1UMR7200, Therapeutic Innovation Lab, Illkirch, France; 2Phophot, Polyphot, Alzachse, Switzerland

Potential involvement of the CCR10/CCL28 axis was recently reported in a murine model of allergic asthma [1]. Blockade of the CCR10 receptor might therefore represent a novel alternative to the current treatment of asthma. We have evaluated the effect of the PEM CCR10 antagonist, POL7085, in an allergic model of asthma in mice. Nine week-old male Balbi/c mice were sensitized to ovalbumin (OVA) administered intraperitoneally in the presence of alum (D0 and D7), and challenged to OVA administered intranasally (D18 to D21). POL7085 was administered once daily 1 hour before each OVA challenge at 9 and 18mg/ml/kg i.nasally (I.N.) or ivexamethasone I.N. (DEX, 2.5nmol/kg) iv vehicle. In vehicle treated animals, OVA induced airway hyperresponsiveness (AHR) as measured by whole body plethysmography, and hypereosinophilia in the bronchoalveolar lavage (BAL) fluid. POL7085 dose-dependently and significantly decreased AHR by 34±16% and eosinophil numbers in BAL by 66±6%. In addition, the higher dose of POL7085 also inhibited IL-5 secretion in BAL (42±13%). IgE and IgG1 synthesis in serum (47±31% and 61±15%, respectively), and lung collagen synthesis (43±11%), although not significantly. POL7085 as compared to DEX also modified body (6.5±1.7% vs 4.5±1.5% for DEX) and spleen weight (24±4% vs 44±3% for DEX).

In conclusion, the PEM CCR10 antagonist, POL7085, significantly and dose-dependently decreased asthma symptoms after once daily local administration in particular AHR and eosinophilia. Blocking the CCR10 chemokine receptor therefore appears as a promising novel approach for treating asthma.

References

4688
Characterisation of TNF-αlectin-like domain derived peptides associated with improved alveolar fluid clearance in pulmonary oedema
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The beneficial effect of the lectin-like domain of TNF-alpha, including the TIP peptide which mimics this domain, on activation of oedema resolution, improved alveolar clearance and protection of lung function after transplantation, is well documented from several independent in vitro and in vivo studies using animal models. The effect is mediated by activation of sodium uptake through the amiloride-sensitive epithelial sodium ion channel (ENaC), which plays a major role in alveolar fluid clearance in normal and diseased lungs. Several peptides mimicking the lectin-like domain of TNF-alpha, and those with greater ability to enhance activation of sodium current through ENaC. No standard therapy exists for pulmonary oedema, thus these TIP peptides represent promising therapeutic agents for activating sodium uptake from the alveolar fluid through ENaC and improving clinical outcome in this condition.

4689
Consequences of chronic pulmonary TLR9 activation in the lung and beyond
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1UMR7200, Therapeutic Innovation Lab, Illkirch, France; 2Leids Universitair Medisch Centrum, Universiteit Leiden, Leiden, Netherlands

Background: Toll like receptor 9 (TLR9) agonist CpG-ODN is being explored as an anti-allergic drug for asthma. However TLR9 could play a role in COPD. Cigarette smoke induced IL-8 production is partly TLR9 mediated.

Aim: To investigate the (extra)-pulmonary effects of CpG-ODN. We hypothesized that pulmonary TLR9 activation induces neutrophil influx which could lead to adverse effects. 

Methods: A single dose of 0.01, 0.05 or 0.25mg/Ml/gBW CpG-ODN was targeted to balbi/c mice lungs by aspiration (acute). Next 0.01mg/Ml/gBW CpG-ODN was administered repeatedly for 5 days (chronic) or 5 weeks (chronic). 24 hours after last exposures, measurements were done: lung function; hypertension and 853s
heart hypertrophy; lung weight; blood and bronchoalveolar lavage (BAL) analysis; morphology of unalvaged lungs.

Results: Total BAL cells were increased in all CpG-ODN mice (p < 0.05). PMNs were increased in blood (30%) and BAL (39%) acute which persistent upon prolonged exposure duration. Blood lymphocytes were subchronically 19% decreased which was reflected in an abundant pulmonary (sub)-chronic lymphocyte influx. Chronic exposure leads to 21% decreased peak expiratory flow (ml/sec) and 71% increased airflow resistance (cm H2O/ml/sec). Right ventricle heart hypertrophy was observed upon chronic exposure; ratio right ventricle weight/total heart weight Cpg-ODN=0.23±0.007; control=0.19±0.008. Wet lung weight was 15.2% increased subchronically and 70.8% chronically.

Conclusion: An interplay between neutrophils and lymphocytes could possibly play a role in TL94 induced adverse pulmonary and cardiovascular effects. Caution is needed when CpG-ODNs are chronically administered for therapeutic purposes.

Acknowledgement TIPharma D1-101

4690

Efficacy of the TRPV1 antagonist SB-705498 in an MRI guinea pig model of rhinitis

Kumar Changanji, Sarah Hotte, Simon Campbell, Kashmira Pindoria, Paula Sakalavala, Diane Cor, Keith Biggadke, Giovanni Vittalli, Jane Denyer. RespLED, GlassSmithKline, Stevenage, United Kingdom

Rationale: Antagonism of nasal TRPV1 receptors is a potential target for inhibition of symptoms associated with rhinitis. Here, we explore the pharmacology of SB-705498 on the contralateral nasal secretory response to ipsilateral nasal capsaicin challenge in the guinea pig.

Methods: Experiments were conducted on intranasally sensitised guinea pigs. Absolute nasal fluid volumes were measured using MRI techniques that provide images of the total nasal cavity of the guinea pig. Animals were pre-treated with SB-705498 or vehicle (-1, -6 and -24h) and MRI scanned to produce first a baseline measurement and then a further measurement at 10 minutes post capsaicin challenge (0.3mM; 50ul).

Results: 1 hour pre-treatment with SB-705498 resulted in approximately 50% inhibition of the secretory response at 10mg/kg (oral; p<0.05). 1mg/kg (intranasal suspension; p<0.005) and 0.1mg/kg (intranasal particle reduced suspension; p<0.0005). At 12 hour pre-treatment, approximately 60% inhibition (p<0.0001) was observed with SB-705498 at 1mg/kg (intranasal particle reduced suspension); at 24h this had reduced to ~50% inhibition (p=0.01).

Conclusion: These studies demonstrate that SB-705498 inhibits capsaicin-induced intranasal parasympathetic responses in guinea pig. Topical application of SB-705498 was associated with a approximately 10-fold reduction in total dose compared with oral administration. In addition, particle reduction of SB-705498 was associated with a further improvement in intranasal potency.

485. Smoking-related disorders

4691

Late-breaking abstract: Effectiveness of easy smoking cessation clinic in tertiary health care settings: Observational study of cohorts

Ratapam Champornot, Maneewan Waikasikorn, Pranomm Maweha, Aninchata Pongphot, Mataneeya Poohkesorn, Jirawat Suwannakit, Thailand

Introduction: Tobacco treatment programs should be offered in clinical settings for all smokers who need to quit smoking. We have co-operated with every units and departments in hospital and changed our service patterns of smoking cessation clinic into easy way. Cessation assistance was provided on working time every day except holiday. It requires approximately 20-30 minutes to complete and involves asking patients about smoking behavior and acting to help them quit. Telephone helpline was used to follow up and encourage smokers trying to continue quit smoking.

Methods: This is an observational study of cohorts of participants in smoking cessation clinic, Buddhist Charaniprayook hospital during June 1 to November 30, 2009. The main outcome measurements were self report abstinence rate at 6 and 12 months, and cost per quit.

Results: Over a period of 6 months, a cohort of 315 patients were enrolled in this study. The self report abstinence rate at 6 and 12 months was 33.7% (106/315) and 27.9% (88/315). The mean cost per quit was 3,145 baht (70 Euro). Lost follow up study. The self report abstinence rate at 6 and 12 months was 33.7% (106/315) and 27.9% (88/315).

Conclusions: In patients under 50 years with PSP the use of cannabis was much higher than in the general population. However, all cannabis users also smoked tobacco. Only 12% of the cannabis users had a normal HRCT (30%). On HRCT, bullae were present in 87% of cannabis users, in contrast to 57% in only tobacco smokers and none in nonsmokers.

4692

LSC 2011 Abstract: Evaluation of morpho-functional changes in airways of young cigarette smokers

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We assumed that even in asymptomatic young smokers, with relatively short smoking duration and normal lung function, induced sputum could be found some changes indicative for early inflammatory process.

Aim: The aim of this study was to evaluate morpho-functional changes in airways of young cigarette smokers.

Method: We enrolled 23±3 years old 12 non-alcoholic smokers (1.59±0.67 pack-years) and 7 healthy non-smoking volunteers. Lung function measurements, sputum induction (IS) and sputum cell analysis were performed.

Results: Demographic data for both study groups did not differ significantly.

Non-smokers and smokers had normal lung function indices. In smokers induced sputum contained statistically significantly (p<0.026) increased relative count of eosinophils 0.923 (0.355-1,753)% compared with non-smokers 0.069 (0.046 - 0.550%). We also found significant reduction of absolute (n=482; p=0.037) and relative (n=682; p=0.004) count of bronchial epithelial cells in induced sputum that correlated to number of smoked pack-years. A trend towards statistical significance showed the correlation between smoking pack-years and the relative number of macrophages in induced sputum (r=0.402; p=0.0872). A trend towards statistical significance was also found in correlation between smoking pack-years and diminished FEV1% of predicted (r = -0.463; p=0.046).

Conclusions: In this study we showed that even smokers with short duration of the smoking habit have already initial signs of inflammation with eosinophil involvement.

4693

Cannabis use in patients with a primary spontaneous pneumothorax

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Introduction: It’s Dutch policy to tolerate cannabis use. In literature active cannabis use is 10% amongst Dutch youth. The association between cannabis use and primary spontaneous pneumothorax (PSP) is unknown.

Aims: To determine the frequency of cannabis use in addition to tobacco smoking in patients with a PSP and to investigate the presence of underlying abnormalities on High Resolution CT (HRCT).

Methods: In a descriptive retrospective study patients were included who presented in a large Dutch teaching hospital with a PSP between August 2008 and August 2010. Because of an increased risk on secondary pneumothorax in older patients, only patients under 50 years were included. Age, gender, BMI, tobacco (T) and cannabis (C) use and (when available) HRCT data were recorded.

Results: In 2 years 53 patients presented with a PSP (42 male, 11 female, mean age 28 years, mean BMI 21). 74% (8% ex) smoked tobacco, 49% (8% ex) used cannabis (cannabis use unknown in 6%). The findings on HRCT are presented in Table 1.

Conclusions: In patients under 50 years with PSP the use of cannabis was much higher than in the general population. However, all cannabis users also smoked tobacco. Only 12% of the cannabis users had a normal HRCT (30%). On HRCT, bullae were present in 87% of cannabis users, in contrast to 57% in only tobacco smokers and none in nonsmokers.

4694

Cigarette smoke induces β2-integrin-dependent neutrophil migration across human umbilical vein endothelium

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Background: Cigarette smoking induces peripheral inflammatory responses in all smokers and is the major risk factor for neutrophilic lung diseases such as chronic obstructive pulmonary disease. The aim of this study was to investigate the effect of cigarette smoke on neutrophil chemotaxis and on β2-integrin activation and function in neutrophilic transmigration through endothelium."
Smoking ages your lungs – Results from the COLD cohort

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Introduction: Reductions in exposure to tobacco smoke was shown to attenuate the risk of exacerbations of chronic respiratory and cardiac conditions both in adults and children. The aim of this study was to compare the changes in emergency department (ED) admissions for smoking-related diseases before and after the implementation of smoking ban in Istanbul.

Methods: Admissions to ten major hospitals in Istanbul in the first five months of 2009 and 2010 were evaluated and compared, using International Classification of Diseases, (ICD-10) diagnostic codes. Results: In 2009, there were 115030 ED admissions for the associated diagnostic codes, whereas this decreased to 87212 in 2010. There was a 16% decrease in acute nasopharyngitis, 32.9% decrease in pneumonia, 18.8% decrease in acute bronchitis, 59.2% decrease in allergic rhinitis, 61.3% decrease in lower respiratory tract diseases, 21.4% decrease in chronic obstructive lung disease, 20.5% decrease in pneumonia, 32.9% decrease in acute bronchitis, 59.2% decrease in allergic rhinitis, 61.3% decrease in lower respiratory tract diseases, 21.4% decrease in chronic obstructive lung disease, 20.5% decrease in asthma, 33.6% decrease in ischemic heart disease and acute myocardial infarction. All differences were found statistically significant. Cost saving of emergency drugs and services on site were 437,104 euros for 10 hospitals in a 5 month period, which is projected to be 3,147,148 euros for Istanbul annually, without calculating the prevented hospital treatment cost.

Conclusion: ER admission rates for diseases associated with active and passive smoking were reduced by 24.2% as a result of smoking ban in Istanbul. Positive effects of clear indoor air ordinances are observed in a very short period, and therefore respiratory health professionals should be advocates for this policies against all odds.
Pulmonary aspergilloma or mycetoma is a ball-shaped fungal infection, which is mostly encountered in pre-existing pulmonary cavities. Local inflammation, high vascularity and pre-existing lung damage can complicate surgical resection. We aimed to describe our patient population, the employed surgical techniques and the postoperative follow-up.

We performed a retrospective analysis of all patients who underwent surgical resection for an aspergilloma between January 2003 and September 2010. Using the patient charts, we examined the clinical data as well as the type of surgical technique that was used. SPSS 17.0 (SPSS INC, Chicago, IL) was used for data analysis.

Twenty-three patients underwent surgical resection for pulmonary aspergilloma. Seventeen (74%) were men, the mean age was 53 years and 43% of the patients presented with hemothorax. Underlying diseases included hematological malignancies (n=8), (a history of) tuberculosis (n=3) and M. Boeckere (n=2). The most frequently employed surgical techniques consisted of wedge resection (n=8), lobectomy (n=7), pneumonectomy (n=2) and segmentectomy (n=2). The duration of the hospitalization after the first surgical resection varied from 5 to 141 days (median 17, IQR: 9-33.25). The median time required for the first surgical resection was 3.4 hours (IQR: 2.34-5.07). Six patients (26%) underwent a rethoracotomy. Four patients died within 6 months after surgery.

Comorbidities were common, the duration of the surgical resections and hospital admissions was long and rethoracotomy was required in 26% of the cases. This illustrates the technical challenges for the surgeon and necessitates treatment in expert centers.

4700
The effect of preoperative albendazole treatment on the cuticular membrane of the pulmonary hydatid cysts
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Background: In this study, the effect of preoperative albendazole treatment on the tensile forces of the cuticular membrane of the pulmonary hydatid cysts is investigated.

Methods: A prospective study on the forty-four patients operated for pulmonary hydatid cysts between January 2009 and November 2010 is planned. The study is approved by the ethics comitee of our centre. Seventeen patients having 20 cysts in the group A operated after three cycles of peroral 10mg/kg/day albendazole treatment where the 27 patients having 29 cysts in group B are operated without any preoperative administration of albendazole. Tensile stress tests were carried out on the excised cuticular membrane for the both groups on the fresh tissue.

Results: The results of this study have shown that the tensile strength of the cuticular membrane of the cysts excised from group A is lesser than group B and the difference between the two groups is statistically significant.

Conclusion: Albendazole treatment decreases the tensile strength of the cuticular membrane of the pulmonary hydatid cysts which may lead to perforation. The patients should be operated as soon as possible without any preoperative medical treatment in order to prevent the complication of the cyst before the definitive surgical treatment.

4701
Comparison between video-thoracoscopic and open surgical management of thoracic empyema
Petros Michos, Athanassios Stamateopoulos, Ioannis Gakidis, Christos Chatziantoniou, Konstantinos Skevis, Demetrios Doltsinis. Thoracic Surgery Department, KAT General Hospital, Athens, Greece

Aim: To evaluate the outcomes of video-thoracoscopic and open surgical management of patients with thoracic empyema.

Methods: We studied 228 patients retrospectively who underwent surgery for thoracic empyema in our hospital between January, 1999 and January, 2011. Patients’ medical records, surgical procedures, and outcomes were reviewed. The study identified 181 affected men and 47affected women with a mean age of 54 years (range 12-90). Presenting symptoms till treatment were 10.26 days (transitional phase empyema). In both groups the most common microorganism was Streptococcus Milleri (33%), following Staphylococcus Aureus (20%) and Gram (-) (10%). Success rate in Group A was 85% and in Group B 20%. In Group B, 40% of the unsuccessfully debrided patients underwent MT mechanical debridement and the rest thoracotomy and decortication. Mean hospital stay in Group A was 4.5days and in Group B 8.5 days. At median follow-up of 8 weeks all Group A patients were symptoms-free with minimal pleural thickening on chest X-ray.

Conclusions: Mechanical debridement by MT is superior to enzymatic debride- ment in the management of thoracic empyema. It is a minimal invasive and effective technique allowing direct visualization of the pleural space and offering a good long-term clinical outcome.
4708 The impact of cardiovascular events in hospitalized patients with community-acquired pneumonia (CAP): Preliminary results from the FAILCAP study
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Background: The 2007 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) guidelines defined severe community-acquired pneumonia (CAP) when patients fulfilled three out of nine minor criteria. Whether each of the criteria is of equal weight is not clear. The purpose of this study was to determine the weight of the minor criteria.

Methods: 1230 adult patients admitted to our hospital from 2005 to 2009 for CAP were enrolled for the study. Severe CAP was defined based on the presence of ≥5% of high-risk patients who fulfilled any of the IDSA/ATS major criteria for severe CAP at the emergency department were excluded.

Results: Hospital mortality rose sharply from 0.3%, 1.0% and 3.3%, respectively, for patients with one, none and two or more minor criteria to 10.5% for patients with three minor criteria. Arterial oxygen pressure/fraction inspired oxygen (PaO2/FiO2) ≤250 mm Hg, confusion, and uremia had the strongest association with mortality (Odds ratio, 22.162, 22.148, 16.343; respectively). Leukopenia, hypothermia, and hypotension were not associated with mortality. Sequential organ failure assessment (SOFA) scores and costs increased significantly with the number of minor criteria present. Uremia and PaO2/FiO2 ≤250 mm Hg were most strongly associated with SOFA scores [rank correlation coefficient (r), 0.352, 0.336; respectively]. PaO2/FiO2 ≤250 mm Hg and confusion were in closest relation to hospital length of stay (LOS) (r, 0.114, 0.114; respectively). PaO2/FiO2 ≤250 mm Hg and multilobar infiltrates were most strongly associated with costs (r, 0.257, 0.196; respectively).

Conclusions: The individual 2007 IDSA/ATS minor criteria for severe CAP were of unequal weight in predicting hospital mortality. SOFA scores, hospital LOS, and costs.

487. Severity, comorbidities and outcomes in community-acquired pneumonia

4705 The results of surgical treatment of patients with tuberculosis of lungs and pleura and diabetes mellitus
Yaroslav Voloshyn, Thoracic, National Institute of Tuberculosis and Pulmonology named F.G. Yanovsky NAMS, Kyiv, Ukraine

Aims: Study results of surgical treatment of patients with tuberculosis of lungs and diabetes mellitus.

Methods: Two groups: main - 301 patients, control – 298.

301 patients were treated in the thoracic department of the institute chemotherapy course (2 months and longer) revealed to be ineffective before reaching the clinic, tuberculosis progressed and complicated diabetes mellitus course and vise versa. Men were 191 (63.45%), women – 110 (36.55%), aged 12-70 years. Had diabetes mellitus and tuberculosis progressed and complicated diabetes mellitus course and vise versa. Men were 191 (63.45%), women – 110 (36.55%), aged 12-70 years. Had diabetes mellitus.

Micobacterial tuberculosis resistant was in 65.21%. Fibrocavernous tuberculosis 40.19%, Tuberculosis - 37.20%, caseous carcinoma - 4.98% were the indications to operation.

Results: After preparation with endotracheal anesthesia 301 patients was operated.

Fibrocavernous tuberculosis 40.19%, tuberculous - 37.20%, caseous carcinoma - 4.98% were the indications to operation.

Conclusions: Surgery remains a crucial adjunct to medical therapy for the treatment of TB and medical failure lesions. We identified temporal changes in the methods of diagnosis and treatment for tuberculosis.

4704 Present forms of the tuberculosis for which surgery is required
Nicolaie Gale1, Cornel Saru1, Vasile Grigore1, Corneliu Petreanu1, Emilia Crisan2, Emilia Tabacu3
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Introduction: With introduction of tuberculostatic drugs, the surgical indications were diminished in the last decades. Althoug, in a country like Romania which touch record level of the tuberculosis’s incidence in time, the surgical approach changed. For example, toracoplasty was abandoned or utilized for selected case. Also, there are new methods of diagnosis which require the surgical approach.

Objectives: The work presents the value of surgery in the diagnosis and in the treatment.

Material and methods: We retrospectively reviewed 67 patients (47 males and 20 females, mean age: 50.2 years) treated between 2008 and 2010. We utilised in diagnosis the mediastinoscopy for mediastinal adenopathies biopsy in 2 cases, videoassisted thoracoscoppy for pleural biopsy in 28 cases. We applied pleuropulmonary deconcretion for 12 patients with lung trapped after adequate medical therapy.

Results: There was one operation-related death (1.5%) and 5 major postoperative complications (7.5%) 22 of 25 of pulmonary resection remained free of TB following surgery. Proportion of comorbidity, Aspergillus coinfection, operation time and emergency were the factors shown to be predictive of an unfavorable outcome.

Conclusions: Surgery remains a crucial adjunct to medical therapy for the treatment of TB. We identified temporal changes in the methods of diagnosis and treatment for tuberculosis.

The aim of this six-years prospecctual cohort study is to compare demographics, aetiology and outcome of patients admitted with pneumonia and categorised as CAP, HCAP and IC.

In conclusion, these data suggest that our IC cohort seem not to be so different from the not-IC patients classified as HCAP by the 2005 ATS/IDSA guidelines. Further investigations are mandatory in order to redesign pneumonia categories.
Cardiovascular events (CVEs) could be detected during the management of hospitalized patients with CAP because of the concomitant hypoxemia and systemic inflammation. The aim of our study was to evaluate incidence, risk factors, and outcomes of hospitalized patients with CAP undergoing CVEs. An international, multicenter, prospective, observational study was performed on consecutive CAP patients hospitalized from October 2009 to November 2010 in 8 Respiratory Units (Clinical Trials: NCT01143155). CVEs were recorded both on hospital admission and during hospitalization. Among the 431 patients enrolled (56±males; mean±SD), the occurrence of CVEs was 20%. The type of CVEs and their incidence is depicted in table.

### Table: CVEs

<table>
<thead>
<tr>
<th>CVEs</th>
<th>Total</th>
<th>On admission</th>
<th>During hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>14 (3) 11 (3) 3 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute cardiogenic pulmonary edema</td>
<td>20 (5) 13 (3) 7 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>30 (6) 27 (6) 19 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term worsening anemia</td>
<td>6 (1) 5 (1) 1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>7 (2) 4 (1) 3 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>10 (2) 3 (1) 7 (2)</td>
<td></td>
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</table>

**Rationale:** The aim was to evaluate serum cortisol as biomarker for the prediction of adverse outcomes independently of the CRB-65 score and inflammatory biomarkers in a large cohort of hospitalized CAP patients.

**Methods:** 894 hospitalized CAP-patients from the CAPNETZ study cohort were included. Serum cortisol was measured and its prognostic accuracy compared to the CRB-65 score, leukocyte count and C-reactive protein. Predetermined endpoints were 30-day mortality and development of critical pneumonia.

**Results:** 64 patients died (6.5%) and 85 developed critical pneumonia (8.6%). Cortisol levels were significantly elevated in both adverse outcomes (p<0.001) and predicted mortality (AUC 0.70 and critical pneumonia (AUC 0.71) independently of all other measured variables including CRB-65 score after logistic regression analysis (p=0.005 and 0.001, respectively). Prognostic accuracy of CRB-65 was significantly improved by adding cortisol levels (combined AUC 0.81 for both endpoints). In Kaplan-Meier analysis, cortisol predicted survival within different CRB-65 strata (p=0.003). In subgroup analyses, cortisol independently predicted critical pneumonia when compared to procalcitonin and minor criteria of the 2007 ATS/IDSA guideline.

**Conclusion:** Cortisol predicts mortality and critical disease in hospitalized CAP patients independently of clinical factors and inflammatory biomarkers. It represents a promising biomarker to complete the available panel of inflammatory, cardiovascular and other biomarkers for risk prediction and should be incorporated into trials assessing optimal combinations of clinical criteria and biomarkers to improve high risk prediction in CAP.

### Table: A population-based study of statin, ARB, and ACE inhibitor use on pneumonia-related outcomes

<table>
<thead>
<tr>
<th>Statin, ARB, or ACE inhibitor use</th>
<th>Total</th>
<th>On admission</th>
<th>During hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
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<td></td>
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**Rationale:** The aim was to evaluate serum cortisol as biomarker for the prediction of adverse outcomes independently of the CRB-65 score and inflammatory biomarkers in a large cohort of hospitalized CAP patients.

**Methods:** 894 hospitalized CAP-patients from the CAPNETZ study cohort were included. Serum cortisol was measured and its prognostic accuracy compared to the CRB-65 score, leukocyte count and C-reactive protein. Predetermined endpoints were 30-day mortality and development of critical pneumonia.

**Results:** 64 patients died (6.5%) and 85 developed critical pneumonia (8.6%). Cortisol levels were significantly elevated in both adverse outcomes (p<0.001) and predicted mortality (AUC 0.70 and critical pneumonia (AUC 0.71) independently of all other measured variables including CRB-65 score after logistic regression analysis (p=0.005 and 0.001, respectively). Prognostic accuracy of CRB-65 was significantly improved by adding cortisol levels (combined AUC 0.81 for both endpoints). In Kaplan-Meier analysis, cortisol predicted survival within different CRB-65 strata (p=0.003). In subgroup analyses, cortisol independently predicted critical pneumonia when compared to procalcitonin and minor criteria of the 2007 ATS/IDSA guideline.

**Conclusion:** Cortisol predicts mortality and critical disease in hospitalized CAP patients independently of clinical factors and inflammatory biomarkers. It represents a promising biomarker to complete the available panel of inflammatory, cardiovascular and other biomarkers for risk prediction and should be incorporated into trials assessing optimal combinations of clinical criteria and biomarkers to improve high risk prediction in CAP.

### Table: A population-based study of statin, ARB, and ACE inhibitor use on pneumonia-related outcomes

<table>
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Inhaled corticosteroids (ICS), systemic inflammatory response and mortality in community-acquired pneumonia (CAP)

Miguel Ferre1, Antoni Torres1, Soledad Reyes2, Raquel Martinez2, Paula Ramírez2, Eva Polverino1, Carlos Agustín1, Juan Cordoba3, Rosario Menéndez1, 1Servicio de Pneumología, Hospital Clínic, Barcelona, Spain; 2Servicio de Neumología, Hospital Universitario la Fe, Valencia, Spain; 3Unidad de Cuidados Intensivos, Hospital Universitario la Fe, Valencia, Spain; 4Servicio de Microbiología, Hospital Universitario la Fe, Valencia, Spain

Background: It was suggested a possible protective effect of ICS in patients with pneumonia. Whether this would be related to modulation of the systemic inflammatory response is unknown. We assessed the relationship between systemic inflammation, ICS and outcome in hospitalised patients with CAP.

Methods: We determined serum levels of C-reactive protein (CRP), Procalcitonin, TNF-alpha, IL-1, IL-6, IL-8 and IL-10 at admission in patients with chronic outpatient treatment with ICS or not, and compared treatment with ICS, biomarkers and other factors potentially related with inflammatory response or mortality in survivors and non-survivors.

Results: We prospectively assessed 663 consecutive patients with CAP, 128 (19%) received outpatient ICS. Patients with ICS were older, had more frequently COPD and asthma, higher PSI and CURB-65 risk classes, less frequently Legionella pneumonia aetiologic, and lower serum levels of TNF-alpha (p < 0.001) and IL-6 (p = 0.0115) as admission. However, hospital mortality was lower for patients treated with ICS (2.1% vs. 3.4%, OR 0.23, 95% CI 0.06-0.99, p = 0.488). After adjusting for age and severity scales, the association of ICS with lower mortality became stronger (adj. OR 0.12, 95% CI 0.02-0.61, p = 0.010), and persisted when even in non-COPD patients (adj. OR 0.07, 95% CI 0.01-0.74, p = 0.027).

Conclusion: Chronic outpatient treatment with ICS was associated with improved survival of CAP possibly due to modulation of patients’ inflammatory response. Whether ICS may improve or not the outcome of patients needs prospective investigation.

Funded: CiberCebes (CB06/060028), 2009 SGR 911, FIS 08/0727-08/0472, Murato TV3 (040530), SEPAR 2003, IDIBAPS.

4713 Steroid titration against mannitol in mild to moderate persistent asthma (STAMINA trial)

Lorna McKlnlay1, Philip Short1, Peter Williamson1, Cathy M. Jackson2, Tom Fordon1, Karine Cleer1, Brian Lipworth1. 1Asthma & Allergy Research Group, University of Dundee, Dundee, United Kingdom; 2Bute Medical School, St Andrews

Objectives: To compare titrating ICS against mannitol airway hyperresponsiveness (AHR) or British Thoracic Society ( BTS) outcomes on asthma control over 1 year in the community.

Methods: After an ICS tapering phase, 157 persistent asthmatics were randomised (parallel) and followed for 1 year. Their subsequent ICS dose (as ciclesonide) was titrated against either mannitol PD10 (AHR strategy) or standard BTS outcomes. Significantly fewer cumulative episodes of loss of control occurred in the AHR rather than BTS group (84 vs 118, p = 0.018), amounting to a 24% lower rate (1.32 vs 1.73 episodes of loss of control/patient/year).

Significant improvements were seen in the AHR group for inflammatory markers including mannitol PD10, methacholine PC20, salivary eosinophil cationic protein (ECP), exhaled nitric oxide, symptoms and reliever use. Final mean inhaled Ciclesonide dose was higher in the AHR group (p < 0.0001) in AHR group: 514 ug vs 208 ug (BTS), with no significant suppression of overnight urinary cortisol/creatinine.

4715 Pathophysiology of airway hyperresponsiveness in patients with nasal polyposis

Bruno Mahut, Laurent Planitier, Brigitte Chevalier-Buisan, Christophe Delclaux. Physiology, Georges Pompidou Hospital, Paris, France

It has been hypothesized that airway hyperresponsiveness (AHR) is characterized by sensitivity (strength of stimulus) and reactivity (responsiveness to stimulus); the latter could be the intrinsic characteristic of AHR. The underlying mechanisms leading to AHR could be 1) airway inflammation, 2) reduction of forces opposing bronchomotor contraction, and 3) structural airway changes/geometry factors. Our main objective was to assess the relationships between reactivity and these three mechanisms using measurements of 1) bronchial and bronchial/alveolar NO, 2) bronchomotor response to deep inspiration, and 3) forced expiratory flows and an index of airway to lung size, i.e. FEF25-75/FVC. Patients with nasal polyposis underwent spirometry, multiple flow measurement of exhaled NO, assessment of bronchomotor response to DI by forced oscillation technique and methacholine challenge allowing the calculation of reactivity (slope of the dose-response curve) and sensitivity (PD10).

One hundred and thirty-two patients with nasal polyposis were prospectively enrolled of whom 71 exhibited AHR. Airway reactivity was correlated with alveolar NO concentration (r = 0.35, p = 0.017), with airflow limitation (FEF25-75%: r = 0.40; p = 0.003) and with an index of airway size to lung size (FEF25-75%/FVC: r = -0.38; p = 0.005), of which only alveolar NO remained the only independent factor in a stepwise multiple regression analysis. Airway sensitivity was not correlated with any pulmonary function or exhaled NO parameter.

Conclusion: In patients with nasal polyposis, the main determinant of reactivity is alveolar NO, suggesting that bronchial/alveolar lung inflammation constitutes one intrinsic characteristic of AHR.

4716 Eosinophilic airway inflammation is heterogeneous in asthma. We recently described a distinct subtype of asthma defined by the expression of genes inducible by Th2 cytokines and with pre-existing ICS dose. This gene signature, which includes periostin, is present in approximately half of asthmatics, and correlates with eosinophilic airway inflammation. However, identification of this subtype depends on non-invasive airway sampling, hence non-invasive biomarkers of this phenotype are desirable.

Objective: Identify systemic biomarkers of eosinophilic airway inflammation.

Methods: We measured fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophil, peroxidin, YKL-40, and IgE levels and compared these biomarkers to airway eosinophils in 5 cohorts of asthmatics across a range of severity (N=150).

Results: We replicated our previous finding of a three-gene bronchial epithelial Th2 signature in a subset of asthmatics and found that peripheral blood eosinophil levels were highly correlated to the gene signature. Blood peroxidin is significantly elevated in asthmatics with evidence of eosinophilic airway inflammation relative to those with minimal eosinophilic airway inflammation despite inhaled corticosteroid (ICS) treatment across a range of disease severity. A logistic regression model including sex, age, body mass index (BMI), IgE, blood eosinophils, FeNO, and serum peroxidin in 59 severe asthmatics showed that, of these indices, serum peroxidin was the single best predictor of airway eosinophilia (p = 0.007).

Conclusions: Peroxidin is a systemic biomarker of airway eosinophilia in asthma and has potential utility in patient selection for emerging asthma therapeutics targeting Th2 inflammation.

488. Phenotyping airway diseases

Francisco, CA, United States; 2Institute for Lung Health, University of Leicester, Leicester, United Kingdom; 3Measuritis-Christborie Laboratories, McGill University, Montreal, QC, Canada

Background: Eosinophilic airway inflammation is heterogeneous in asthma. We recently described a distinct subtype of asthma defined by the expression of genes inducible by Th2 cytokines and with pre-existing ICS dose. This gene signature, which includes periostin, is present in approximately half of asthmatics, and correlates with eosinophilic airway inflammation. However, identification of this subtype depends on non-invasive airway sampling, hence non-invasive biomarkers of this phenotype are desirable.

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Conclusions: Peroxidin is a systemic biomarker of airway eosinophilia in asthma and has potential utility in patient selection for emerging asthma therapeutics targeting Th2 inflammation.
Conclusions: Managing patients in primary care using mannitol to guide ICS therapy resulted in significant reductions in episodes of loss of control, symptoms and reliever use, along with suppression of inflammatory markers but not adrenal function.

4717 Preparing asthmatic patients to climb to extreme high altitude (asthma Aconcagua expedition)

Sven Seys¹, Marc Daenen², Lieven Dupont³, ¹Internal Medicine, Katholieke Universiteit Leuven, Leuven, Vlaams-Brabant, Belgium; ²Internal Medicine, Hospital of Oost-Limburg, Genk, Limburg, Belgium

A group of 18 asthmatics were evaluated in preparation for an expedition to climb the Aconcagua mountain (6900m).

Patients were evaluated at different time points before expedition: screening visit, hypoxia chamber and cold air exposition (in an attempt to simulate conditions at extreme altitude) as well as before/after the expedition. During the hypoxia simulating experiment, patients stayed for 30 min in a chamber filled with 11% oxygen followed by a maximal exercise test. During the cold air exposition, patients resided for 24 hours in an indoor ski resort (mean temperature of -8 °C).

All patients except one (score of 18/25) had an ACT well controlled asthma (ACT > 20). During one year of preparation, FeNO values significantly reduced (p=0.01) while lung function parameters remained stable. FEV1 and FeNO values were slightly but significantly lower (mean change in FEV1 of 2.7%, p=0.01 and mean change in FeNO of 2.2 ppb; p=0.03) after a maximal exercise protocol under hypoxic conditions (FeO2=11%). A significant decrease in FEV1 was also observed after a 24h stay at -8 °C (mean change of 6.6%, p=0.009). This was accompanied by an increase in sputum neutrophils (13% pre versus 48.6% post, p<0.01) but was not associated with a change in FeNO levels (p=0.07).

During one year of preparation prior to climbing the Aconcagua mountain, there was an improvement in airway inflammation despite adequate asthma control at baseline. Exercising in hypoxic conditions (60 min, FeO2 11%) induced a minor decrease in FeV1 and FENO in asthmatics. Exposure of asthmatic patients to cold air for 24h resulted in a larger decrease in FEV1, which was associated with a neutrophilic airway inflammation.

4718 Inflammatory subtypes of non-atopic asthma

J.C. de Groot¹, H. Storm², E.H. Bel³, A. ten Brinke³, ¹Respiratory Medicine, Medical Centre Leeuwarden, Leeuwarden, Netherlands; ²Clinical Chemistry, Medical Centre Leeuwarden, Leeuwarden, Netherlands; ³Respiratory Medicine, Academic Medical Centre, Amsterdam, Netherlands

Introduction: In asthma, several types of airflow inflammation have been described (Simpson Respirology 2006), which may represent clinically different subtypes of asthma. Whether non-atopic asthma can also be divided into different subtypes according to airflow inflammation is unknown.

Aim: To investigate whether different inflammatory profiles correspond with distinct clinical and functional characteristics in patients with non-atopic asthma.

Methods: In a cross-sectional study we included outpatients with non-atopic asthma and divided them into 4 types of airflow inflammation. All patients filled out questionnaires (co-morbidity, ACQ, AQLQ, Sino-Nasal outcome Test (SNOT)) and underwent spirometry, blood tests, sputum induction and nasal endoscopy.

Results: 62 patients (92% adult onset) were included. We found no differences in BML, questionnaires or spirometry. Differences between groups are: see Table 1.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Eosinophils &gt; 3%</th>
<th>Neutrophils &gt; 64%</th>
<th>Both eosinoto</th>
<th>Non eosinoto</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male%</td>
<td>77</td>
<td>30</td>
<td>0</td>
<td>27</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>59 (10.3)</td>
<td>53 (15.2)</td>
<td>57 (11.2)</td>
<td>49 (14.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Auto-immune</td>
<td>8</td>
<td>44</td>
<td>67</td>
<td>18</td>
<td>0.03</td>
</tr>
<tr>
<td>IgE median, range</td>
<td>180 (23–2110)</td>
<td>13 (1–243)</td>
<td>30 (5–133)</td>
<td>15 (3–88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PC20 median</td>
<td>2.5 (0.3–9.8)</td>
<td>6.7 (0.6–9.8)</td>
<td>0.02 (0.2–9.8)</td>
<td>3.6 (0.2–9.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Nasal polyps, %</td>
<td>39</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Auto-immune = DM, thyroid dysfunction, reumatoid arthritis and other.

Conclusion: Almost all adult non-atopic asthma patients have their onset of asthma in adulthood. There are at least 2 distinct phenotypes: an eosinophilic phenotype, characterized by male gender, high levels of IgE and nasal polyps, and a neutrophilic phenotype associated with extra-pulmonary auto-immune diseases.

4719 The role of food allergy in adult onset asthma

M. Amelink¹, S.B. de Nijjs², P. van Spiegel³, F.H. Krouwels¹, E.J.M. Weersink¹, A. ten Brinke¹, F.J. Sterk³, E.H. Bel³, ¹Respiratory Medicine, Academic Medical Centre, Amsterdam, Netherlands; ²Respiratory Medicine, Slotervaart Hospital, Amsterdam, Netherlands; ³Respiratory Medicine, Maastricht University, Maastricht, Netherlands

Background: Adult onset asthma is a poorly characterized phenotype of asthma. Whereas in childhood-onset asthma food allergies are closely related to the development of asthma (Zeiger JACI 1995), this relationship has never been studied in adult onset asthma. We hypothesize that food allergies are present in adult onset asthma, in particular in patients with high levels of total IgE.

Aim: To investigate the presence of specific IgE antibodies against a panel of common food and aeroallergens in patients with adult onset asthma, and to relate this to clinical, lung function and inflammatory markers.

Methods: In 150 patients (65% female; age 52.3 ± 13.5y) specific IgE against food allergens (milk, soy, cod, peanut, ovalbumin, wheat), aeroallergens (house dust mite, cat, dog, tree, grass, herbs, mould), total IgE, FeNO and spirometry were cross-sectionally compared between patients with and without (food) allergies.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Non-atopic (n=81)</th>
<th>Atopic (n=67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.1 (11.8)²</td>
<td>51.9 (10.5)²</td>
<td>0.3</td>
</tr>
<tr>
<td>Male gender%</td>
<td>36</td>
<td>36</td>
<td>0.94</td>
</tr>
<tr>
<td>Asthma severity%</td>
<td>51</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Nasal polyps%</td>
<td>52²</td>
<td>32</td>
<td>0.053</td>
</tr>
<tr>
<td>Total IgE‡</td>
<td>50 (2–1068)</td>
<td>226 (17–2076)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>0.19 (0.02–0.92)</td>
<td>0.26 (0.05–1.17)</td>
<td>0.053</td>
</tr>
<tr>
<td>Exhaled NO³</td>
<td>48.5 (55.6)</td>
<td>44.9 (40.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>FeNO¹</td>
<td>90.8 (21.4)</td>
<td>91.8 (20.3)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

‡Mean (SD); *Median (range); °p < 0.05 atopic with food allergy vs non-atopic; †p < 0.05 non-atopic vs atopic.

Conclusions: 10% of patients with adult onset asthma have food allergies. These patients have higher levels of total IgE and are more often males. This implies that screening for food allergies in patients with adult onset asthma and high levels of IgE is warranted.

4720 Expression of prohibitin 1 mitochondrial protein in non-COPD and COPD smokers

Nikolaos Soulitzis, Eirini Neofytou, Maria Paurou, Sotiris Menikou, Nikolaos Siafakas, Elemi Tzotzaki. Laboratory of Molecular and Cellular Pulmonology, Medical School, University of Crete, Heraklion, Crete, Greece

Introduction: Prohibitin (PHB1) is a versatile protein that is located in the inner mitochondrial membrane, maintaining normal mitochondrial function and morphology. Prohibitin interacts with NADH dehydrogenase, a protein complex essential for the oxidoreductase activity within cells. However, its expression in lung epithelium, especially in patients with inflammatory lung diseases associated with increased oxidative stress, such as COPD, is unknown.

Aim: To study PHB1 expression in lung tissue of non-smokers, non-COPD smokers and COPD patients.

Methodology: Lung tissue specimens from 30 male subjects were studied: 15 COPD patients [age: 65.9±6.2 years, smoking: 88.9±51 pack-years, FEV1 (% pred: 58.4±16.4, FEV1/FVC (§%): 66.2±8.6], 10 non-COPD smokers (age: 57.0±11.7 years, smoking: 67.1±3.99 pack-years, FEV1 (% pred: 84.0±15.9, FEV1/FVC (%): 80.0±3.8) and 5 non-smokers. Quantitative Real-Time PCR and Western Blot experiments were carried out for PHB1, using beta-actin as internal control.

Results: Non-COPD smokers exhibited lower prohibitin levels when compared to non-smokers (0.55±0.06 vs 0.90±0.06, p=0.011), while PHB1 mRNA levels were even further decreased in COPD patients (0.32±0.03), a finding statistically significant vs. both non-COPD smokers (p=0.012) and non-smokers (p=0.009). Western blot analysis verified the above results (non-smokers: 1.77±0.10, non-COPD smokers: 0.97±0.08, COPD patients: 0.62±0.09, p=0.028).

Conclusion: The significantly downregulated prohibitin levels in non-COPD and COPD smokers in comparison with non-smokers possibly reflects a distorted mitochondrial function, resulting in decreased anti-oxidant activity, especially in the mitochondria of COPD patients.
Biomarker discovery in chronic obstructive pulmonary disease (COPD) using epithelial lining fluid: A proteomic approach

Lorenza Franciosi1, Natalia Govershchina1, Fabrizia Fusetti2, Bert Poolman3, Nick ten Hacken3, Dirkje Postma3, Rainer Bischoff3.

1Analytical Biochemistry, University of Groningen, Groningen, Netherlands; 2Department of Biochemistry, NPC Research Hotel, University of Groningen, Groningen, Netherlands; 3Department of Pulmonary Disease, Groningen Research Institute of Asthma and COPD, University Medical Center Groningen, Groningen, Netherlands

Aim: To discover proteins that change in abundance in ELF (Epithelial Lining Fluid) from COPD patients versus healthy controls using a quantitative proteomics approach.

Methods: The ELF proteome from COPD patients and healthy controls was studied by 1D polyacrylamide gel electrophoresis followed by in-gel tryptic digestion to assess the feasibility of such an approach. 40 gel slices were obtained from each lane of the gel (corresponding to one patient). Digested samples were analyzed by nanoChip-LC-MS/MS using an ion trap. We performed a quantitative pilot study of ELF from 4 COPD patients and 4 healthy controls [table 1] to test for statistically significant differences in protein levels. ELF samples were digested by trypsin, labeled with stable isotope-containing reagents (iTRAQ®; 8-plex) and processed by strong cation-exchange chromatography followed by nanoLC-MS/MS. In order to validate the results, a second quantitative analysis of an independent sample set (4 COPD vs 4 healthy) using the same methodological approach was done.

Results: The 1D electrophoretic approach resulted in more than 500 identified proteins. Most of the identified proteins were present in both COPD and healthy samples, although some proteins were only identified either in healthy control or in COPD samples. The quantitative studies showed a number of proteins significantly different between ELF of COPD patients and controls, including 4 up-regulated proteins in common in both studies.

Conclusions: The obtained results show the possibility to discover proteins differentially expressed in ELF of COPD patients and controls. We are currently validating these proteins by western blot and immunohistochemistry.

489. Continuous medical education

Training requirements for respiratory physicians performing ultrasound-guided transesophageal fine needle aspiration (EUS-FNA) for mediastinal staging

Lars Konge1, Inoue Annema2, Paul Clementsen3, Peter Vilmann3, Charlotte Ringsted1.

1Centre for Clinical Education, University of Copenhagen, Copenhagen, Denmark; 2Department of Pulmonology, Leiden Medical Centre, Leiden, Netherlands; 3Department of Pulmonology, University Hospital of Copenhagen Gentofte, Gentofte, Denmark

Accurate mediastinal nodal staging is important for patients with resectable non-small cell lung cancer. EUS-FNA is an alternative to mediastinoscopy, but EUS training requirements are under discussion. The purpose of this study was to explore the amount of training needed to establish basic competency in EUS-FNA.

Five experienced respiratory physicians from Denmark and the Netherlands were included in the study (3 men, 2 women). They had no prior experience in EUS. Each participant completed between 20 and 30 supervised EUS-FNA procedures. All procedures were video-recorded and blindly and independently assessed by three experts using a validated assessment tool.

Data will be presented as individual and averaged learning curves. Currently the first participant has finished training and her learning curve is presented in the figure below. Differences in the acquisition of skills between trainees will be presented. Preliminary data suggest that performance of approximately 25 procedures secures basic competence in EUS-FNA for mediastinal staging.

4723

A Delphi study to create grade-specific competencies for a trust-wide non-invasive ventilation training programme

Anand Shah, Roger Sharpe, Thungo Kuwani.

Postgraduate Medical Education, North West London Hospitals Trust, London, United Kingdom

Introduction: Non-invasive ventilation (NIV) is an expanding treatment modality for respiratory failure and is increasingly used in non-specialist acute areas. Although comprehensive national guidelines exist, there is no consensus as to the expected level of competency for non-specialist health professionals. We used a modified Delphi process to create grade-specific NIV competencies which were then used to structure a comprehensive grade-based training programme.

Method: A 3 round Delphi process was used with an expert panel of 20 respiratory consultants, registrars, physiotherapists and nurses. A provisional list of competencies was created following amendment by the expert panel of an initial draft formulated by literature and peer review. In the second round, competencies were added or deleted following statistical analysis of grade-based relevancy rating using a 6-point Likert scale. Competencies where consensus was not reached were present in the third round alongside expert viewpoint. Competencies with no consensus following 3 rounds were deleted. The finalised lists were sent to a selection of each grade for self-assessment of competency.

Results: A high variability was noted in competency expectation amongst our expert panel. Self-assessment showed gross lack of competency amongst junior doctors and nurses with high variability at specialist trainee level.

Conclusion: Competencies were used to create a grade-based training programme with objective trainee learning outcomes. The study revealed a high level of inconsistency regarding expectation amongst NIV specialists alongside exposing the lack of current formal NIV training and weaknesses of an apprenticeship model.

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A survey of intensive care medicine training for respiratory specialist trainees in the United Kingdom

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4725
Special interest training in respiratory medicine across Yorkshire: A web based survey
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Introduction: The Joint Royal Colleges of Physicians Training Board (JRCPTB) published the training curriculum for Respiratory Medicine in August 2010. It identified areas of special interest enabling the trainee to undertake additional training. However, this is not formally recognized and there is no centrally agreed funding. Current options available for such training include as Out Of Programme Experience (OOPE) or during research into the subject area concerned.

Aims: To understand the current special areas of interest among trainees in Respiratory Medicine across Yorkshire, United Kingdom.

Method: A web-based questionnaire was designed and all the trainees (n=75) in the Yorkshire region were invited to complete the survey.

Results: The response rate was 52% (n=39). 69.2% (n=27) had a special area of interest.

Conclusion: Majority of the trainees wish to specialize in a specific area of interest but there seems to be a lack of funding and training opportunities in the form of fellowships. Improving the current training curriculum will lead to better patient care and service provision in the National Health Service.

4726
Attitude of chest physicians working in provincial state hospitals, in Turkey toward continuous medical education
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Introduction: Continuing medical education is carried out primarily by medical associations. Bulletins are published on method.

Aim: To investigate post-training status and trends regarding this issue of chest physicians working in provincial state hospitals

Methods: Questionnaires, that consist of 18 questions about years of work, institution, participation in congresses and training activities, regular follow-up of publications and web sites, views about post-training; with permission of Ministry of Health; was sent to chest physicians. Participants, completed the questionnaire and sent back anonymously.

Results: 85 of 130 chest physicians in 36 provinces participated. Response rate was 65%. Average working years was 15.0±8.40. 44.7% were working in state hospitals and 54.1% were in chest disease hospitals. Participation to congresses on last 2 years was 3.59±1.62. 28.2% were attending education meetings regularly. 38.8% answered question of “Do you follow a publication regularly?” with “No”. Participants who do not follow the web sites was 34.1%. While years of work increased, follow-up of web sites decreased (p=0.00). Question of “Do you feel yourself declined in terms of professional information and facilities sometimes?” replied “Yes” by 58.8%.

Conclusion: We found that our colleagues have been less interested in training activities. Training activities, independent of personal initiatives, will increase self-confidence and professional qualifications.

4727
Developing respiratory services – What are the needs of the respiratory clinician leaders and what can a short course deliver?
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Background: The development of services within health care systems is complex and requires expertise in clinical, economic and managerial issues. Within the UK, clinicians are being expected to work with managers and commissioners to develop services. This newly recognised area of work requires personal development. An ongoing programme of learning was developed to support respiratory leaders in this increasingly challenging role.

Method: The PCRS-UK have developed bi-annual courses to support clinical respiratory leaders in understanding the many issues that are required to enable the leader to influence service development and to support their own teams in changing services in line with best medical evidence. The course evaluations have provided useful information on areas that clinicians wish to develop as they move into leadership roles and demonstrate the potential development from attending a short course.

Results: 64 participants completed the most recent course. Around 2/3 of delegates provided feedback on their skills/confidence. This demonstrated widespread requirements in both understanding NHS policy and direction as well as core leadership skills (understanding others, developing groups, organising and chairing meetings, communicating with commissioners). The course achieved considerable improvements in confidence and skills in most of these areas.

Conclusions: There is a clear need to support the clinical respiratory leaders of the future who have considerable developmental needs to complement their clinical expertise. The areas for this can be identified and a relatively short and focused course can make a significant impact on these needs.

490. Physiological basis of respiratory disease

490.1 Physiological basis of respiratory disease

P4728
Late-breaking abstract: Comparative analysis of cardiopulmonary and clinical responses to six minute walking test and maximal exercising test in obese women
Luziana Di Thommā­ mar-Luporini, Sorea Plon Jurgensen, Viviane Castello, Camila Negrão Dias, Rafael Luis Luporini, José Carlos Bonjorno-Júnior, Claudio Ricardo de Oliveira, Aparecida Maria Catui, Audrey Borghi-Silva. Phsyiotherapy, Federal University of Sao Carlos, Sao Carlos, Brazil; Medicine Department, Federal University of Sao Carlos, Sao Carlos, Brazil; Catholic University of Pernambuco, Pernambuco, Brazil

Background: The six minute walk test on the treadmill (tread6MWT) can be an efficient method to evaluate the functional capacity in obese population comparable to cardiopulmonary exercising test (CPET).

Aims: To compare the cardiopulmonary and subjective responses to tread6MWT and CPET in obese and eutrophic women.

Methods: Fourteen obese women were recruited to obese group (OG) and 15 women to eutrophic group (EG). Both groups performed a CPET and a toss6MWT. Cardiopulmonary variables and dyspnea level were registered. Absolute limits of agreement between cardiopulmonary and subjective responses to CPET and toss6MWT were assessed by Bland-Altman analysis.

Results: OG presented higher oxygen uptake (V'02), minute ventilation (V'E), and systolic blood pressure (SBP) than EG (p<0.05) in both tests. There is a
strong correlation (p=0.76) between VO2 and body mass index in the CPET, as well as heart rate (HR) in the peak of both tests (r=0.77) in OG. The dyspnea was higher during CPET than treadmillMT (p=0.05) in both groups. It was observed the agreement of both tests to identify relative VO2, VE, SBF and HR at the peak of exercise, presenting a mean difference between the tests of: 0±6.5 (mL/kg/min), 29±1.69 (L/min), 17.5±1.94 (mmHg) and 32.9±1.94 (bpm), respectively ([BHAS.ISD]).

Conclusions: The treadmillMT was able to promote metabolic and cardiopulmonary responses in agreement to the CPET. The treadmillMT seems to be an appropriate method to evaluate the functional limits and lactic acidosis in obese women without submitting them to such a significative dyspnea as the CPET does.

Financial support: FAPESP (09/01842-0) and CAPES.

P4729
Late-breaking abstract: Time-dependent effect of acute hypoxia on brain excitability in healthy humans
Samuel Verges1, Thomas Rupp1, Marc Jabeau2, Bernard Wuyam1, Stéphane Perrey1, Patrick Levy1, Guillaume Miller1,2
HP2 Laboratory, U1042, Joseph Fourier University, INSEERM, Grenoble, France; 1Exercise Physiology Laboratory, Jean Monnet University, Saint-Etienne, France; 2Movement To Health Laboratory, Montpellier-1 University, Montpellier, France

Some studies have shown altered cortex excitability in hypoxemia patients suffering from COPD or OSAS. Recently, contradictory results regarding the effect of hypoxia (H) on cortex excitability have been reported in healthy subjects, possibly depending on the methodologies used. We evaluated the effects of 1 and 3 hours H on motor cortex excitability, intracortical inhibition and supraspinal voluntary activation (VA) using transcranial magnetic stimulation (TMS). TMS to the quadriceps area and femoral nerve electrical stimulations were performed in normoxia and H (FiO2 = 12%) in 10 healthy subjects. Motor-evoked potentials (MEPs) at 50-100% maximal voluntary contraction - MVC), cortical silent periods (CSP) and VA were measured. One hour H did not modify any parameters of brain excitability but reduced VA probably due to the repetition of contractions 1-h apart (98.2± vs. 95.2±%; p<0.01). Conversely, 3 h significantly increased i) MEPs of the rectus femoris (RF) at all force levels (±12%), vastus lateralis (VL) and vastus medialis (VM) at all force levels (e.g. at 50% MVC, RF: +26±35%, VL: +15±24%, VM: +17±15%) and ii) stimulator power output (s.g. at 70% maximal power, RF: +17±23%, VL: +37%, VM: +15±19%) and modulated cortical silent periods (CSP) at all force levels (e.g. at 50% MVC, RF: +23±39%, VL: +27±31%, VM: +24±37% (all p<0.05), but did not modify VA (98.1±% vs. 97.2±%; p=0.21). These data demonstrate a time-dependent H-induced increase in cortex excitability and intra-cortical inhibition, without changes in VA. The decrease of cortical and/or physical or cognitive performance needs to be elucidated to better understand the effects of hypoxemia in patients.

P4730
Late-breaking abstract: Association between serum surfactant protein D (SP-D) and lung function measurements in self-reported healthy twins
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Introduction: Serum SP-D is suggested to serve as a biomarker in various pulmonary diseases, and has been showed negatively correlated to FEV1 in COPD. Aim: The objective of the present study was to investigate the association between serum SP-D and lung function in normal Danes.

Material and methods: Data of serum SP-D originates from 1,476 self-reported healthy adult twins. Association between variables were analyzed by using a multiple linear regression model using SP-D as response variable and pre-bronchodilatator FEV1 and FVC as explanatory variables. Intra-pair dependency was taken into account, and data was adjusted for sex, age and BMI.

Results: There was a significant difference in mean serum SP-D levels in smokers and with or without obstruction. (p<0.05) See table 1. The association for SP-D with FEV1 and FVC was found to be negative in smokers (p=0.001/0.001), but positive in non-smokers (p=0.030/0.002).

<table>
<thead>
<tr>
<th>SP-D</th>
<th>FEV1% pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (N=911)</td>
<td>966±490</td>
</tr>
<tr>
<td>WO (N=38)</td>
<td>1347±753</td>
</tr>
<tr>
<td>NO (N=417)</td>
<td>966±490</td>
</tr>
<tr>
<td>WO (N=48)</td>
<td>1347±753</td>
</tr>
</tbody>
</table>

Conclusions and perspectives: Findings indicate opposite phenotypic correlation between SP-D and FEV1 in smoking and non-smoking individuals. Further analysis of available data will include multivariate twin modelling to investigate whether there is a genetic correlation between the traits and genetic association analysis to find out whether such a genetic correlation could be explained by single nucleotide polymorphisms within candidate genes such as the SPFDP gene.

P4731
Late-breaking abstract: Determination of anaerobic threshold through different methodologies during ramp protocol in elderly healthy men
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For assessing the cardiopulmonary integration during aerobic exercise, anaerobic threshold (AT) has been an important index of performance. Additionally, the respiratory compensation threshold (RCT) has been used for determining performance of quasi-maximum intensities (Wasserman et al., 1983). The aim of this study to identify the anaerobic threshold (AT) obtained from the V-slope method, visual inspection of oxymoglobin (O2Hb) and deoxymoglobin (HbH) curves and compare findings with the heteroscedastic (HS) method applied to VCO2, heart rate (HR) and HbH data. Fourteen healthy men were subjected to cardiopulmonary testing (CPX) on a cycle-ergometer until physical exhaustion. Biological signals collected during CPX included: ventilatory variables; spectroscopy by NIRS; and HR by a cardiofrequency meter. We observed temporal equivalence and similar values of power, VO2 (mL/min), VO2 (mL kg^-1 min^-1) and HR at AT by the detection methods exposure described in addition by the Blomqvist-Alman plot (Fig. 1). HR confirmed the good agreement between the methods with biases between -1.3 and 3.5 bpm.

In conclusion: (i) all detection methods were sensitive in identifying AT, including the HS applied to HR and ii) the methods showed good correlation in the identification of AT. Thus the results support the HR seems to be a valid parameter in determining the AT of the individuals in our study (Grants: FAPESP)

P4732
Cytokine expression in the diaphragm of rats breathing against subacute hypoxic conditions
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COPD patients show muscle damage and an increase in the expression of local cytokines in their diaphragms. The paracrine role of these cytokines still remains controversial.

Objective: To analyze the effects of subacute hypoxia on the diaphragm muscle.

Methods: Wistar rats (n=8/group) were exposed to: (1) hypoxia (FIO2 0.10) +placebo, (2) normoxia +placebo, (3) hypoxia +Infliximab [monoclonal antibody that results in the blockade of TNF-a receptors], and (4) normoxia +Infliximab for 2 weeks in all cases. At the end of the study period diaphragm and gastrocnemius muscles as well as blood samples were obtained. Molecular and cellular indices of muscle damage, oxidative stress, cytokine expression and activation of regeneration pathways were obtained using morphometry, Western-blot, spectrophotometry, ELISA, luminometry and RT-PCR.

Results: Although rats exposed to hypoxia showed higher levels of expression of different cytokines (TNF-a, IL-6, INF-g) in their diaphragms than the control animals (normoxia), no differences were observed in muscle damage, oxidative stress and biomarkers of muscle regeneration. Inhibition of TNF-a action in hypoxic animals resulted in an even higher expression of local cytokines with no relevant changes in the other variables when compared with hypoxic animals receiving placebo. No changes were observed in either limb muscle or blood in any of the groups.

863s
Conclusions: Hypoxia induces local inflammation in respiratory muscles of hypoxic rats. This effect appears to be selective for respiratory muscles and can be related to changes in their mechanical loading and its mismatching with the oxygen delivery to the muscle.

Funded: SAF07-62719, CIBERES, SEPAR & SOCAP

P4733 The impact of aerobic exercise on lung inflammation and remodeling in experimental emphysema

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This study investigated the impact of aerobic exercise on lung inflammation and remodeling in experimental emphysema. 32 mice were randomized into 2 groups. In control (C) animals, saline was intratracheally (i.t.) injected, whereas emphysema mice received porcine pancreatic elastase (ELA, 0.1 U, i.t.). Saline and ELA were i.t. injected once a week for 4 weeks. After the last week, C and emphysema groups were further randomized into subgroups: sedentary and exercise. Exercise mice ran on a motorized treadmill, at moderate intensity (8-12 m/min), 5% grade, 30 min/day, 3 times a week for 4 wk. 24-h after the last session, lung mechanics and morphometry, as well as cytokines and total cell count in bronchoalveolar lavage fluid (BALF) and blood were measured. Echocardiographic analysis was done before and after emphysema induction and at the end of the experiment. The sedentary emphysema group presented, compared to C: 1) increased lung static elastance, 2) increased lung hyperinflation and elastic fiber content; 3) augmented levels of KC [murine interleukin (IL)-8 homolog], tumor necrosis factor-α, interferon-γ, and IL-10; and 4) pulmonary arterial hypoxia, evidenced by increased pulmonary flow acceleration. Aerobic exercise: 1) improved lung mechanics, 2) reduced lung hyperinflation, and the number of cells and levels of these cytokines in BALF and blood, 3) diminished elastic fiber content, and 4) restored pulmonary flow acceleration to C values. Conclusion: in this model of lung inflammation and emphysema, 4 weeks of aerobic exercise modulated the inflammatory process and acted on lung remodeling, improving pulmonary function. Supported by: INCIT/INOFAR, FAPERJ, PRONEX, CNPq

P4734 Regular and moderate exercise prevents airway remodeling in a murine model of chronic allergic asthma

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The present study investigated whether regular and moderate aerobic exercise might prevent airway remodeling in experimental chronic allergic asthma. For this purpose, 48 BALB/c mice were assigned into 2 groups: sedentary (S) and trained (T). Tr group ran on a motorized treadmill, at moderate intensity (8-12 m/min); 5% grade, 30 min/day, 3 times a week for 8 wk. At 8 wk, animals were further randomised into 2 subgroups: immunized and challenged with ovalbumin (OVA) or to receive saline using the same protocol (C). Aerobic exercise continued until the end of the protocol. Echocardiographic analysis was done before, at 4 and 8 weeks of treatment, and after asthma induction. Twenty-four hours after the last challenge, trained, compared to sedentary mice, presented: 1) an increase in systolic output, left ventricular mass, and end-diastolic volume; 2) a reduction in airway resistance, viscoelastic pressure, static elastance, eosinophil infiltration, smooth-muscle actin expression, and collagen fiber content in airways and lung parenchyma; 3) a decrease of transforming growth factor-β levels in bronchoalveolar lavage fluid (BALF) and blood; 4) an increase in interferon-γ in BALF and blood; 5) an augment of interleukin (IL)-10 in blood but a reduction in BALF; and 6) a decrease in IL-5 and IL-13 only in BALF. In conclusion, regular and moderate aerobic exercise was effective in preventing airway and lung parenchyma remodeling in the present murine model of chronic allergic asthma, improving lung function. Supported by: INCIT/INOFAR, CNPq, PRONEX, FAPERJ, CAPES

P4735 Repeated mannitol or NaCl hyperosmolar exposure of bronchial epithelial cells to mimic exercise-induced airways damage

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Hyperosmolarity of the airway surface lining fluid might be involved in exercise-induced airway epithelial damage. Hypersomolarity causes release of interleukin 8 (IL-8) by bronchial epithelial cells (BEC) in vitro, but the effects of repeated hyperosmolar exposure on BEC are unknown. 16HBE cells were exposed to NaCl or Mannitol (Mann) (320, 640, 960, 1280 mOsm/kg H2O) in culture medium for 0 or 40 min for 3 consecutive days; at 24 h after each exposure, supernatants were collected and stored at -80 °C for subsequent IL-8 measurements (R&D System, UK). Cell viability was examined by MTT assay. Cell viability (p<0.001) was assessed by Western Blot. Repeated exposure to NaCl or Mann for 10 min at any concentration did not affect IL-8 release. Exposure of 16-HBE cells to NaCl or Mann at 640-1280 mOsm/kg H2O for 40 min increased IL-8 concentration at days 1 and 2 compared to untreated cells (p<0.0001); however, IL-8 release decreased at days 2-3 compared to day 1 (p<0.05). Repeated NaCl or Mann treatment for 10 min decreased cell viability by 10-20% (p<0.0001), while hyperosmolar exposure for 40 min decreased cell viability in a dose-dependent manner at day 1 and dramatically at days 2-3 (60% for NaCl, 40% for Mann at highest concentrations, p<0.0001). NaCl was cytotoxic compared to Mann (p<0.05). PINK expression increased dose-dependently with hyperosmolarity at days 1-2 (increased at day 3; IL-8 release was blocked by a specific JNK inhibitor (SP600125). Therefore, hyperosmolar exposure acutely activates BECs through JNK activation, whereas no changes were observed in mannitol exposure repeated for 3 days decreased IL-8 release likely due to major epithelial damage.

P4736 Acute exposure to mechanical forces deteriorates lung structure and function in a mouse model of emphysema

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Mechanical forces have been suggested to accelerate the deterioration of lung structure and function in emphysema. To test this, we used C57BL/6 mice treated with porcine pancreatic elastase (N=48) or left intact as controls (N=16). At 2, 7 or 21 days after treatment, mice were ventilated (V=8 ml/kg, 240/min) for 1 h with or without deep inspiration. In the post-inspiration period, at the end of breath, fluid (BALF) and blood were measured. Echocardiographic analysis was done before and after emphysema induction and at the end of the experiment. The sedentary emphysema group presented, compared to C: 1) reduced lung static elastance; 2) increased lung hyperinflation and elastic fiber content; 3) augmented levels of KC [murine interleukin (IL)-8 homolog], tumor necrosis factor-α, interferon-γ, and IL-10; and 4) pulmonary arterial hypoxia, evidenced by increased pulmonary flow acceleration. Aerobic exercise: 1) improved lung mechanics, 2) reduced lung hyperinflation, and the number of cells and levels of these cytokines in BALF and blood, 3) diminished elastic fiber content, and 4) restored pulmonary flow acceleration to C values. Therefore, our results suggest that acute mechanical forces rupture septal walls with a subsequent increase in FRC and a decrease in small airspaces diameters in a time dependent manner during disease progression. Supported by grants NIH HL090757 and OTKA 66700.

P4737 Aerobic exercise training attenuates the decrease in heart rate variability induced by exposure to cigarette smoke in mice

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Smoking has been shown to influence the tone of the autonomic nervous system as reflected by heart rate variability (HRV) a predictor of increased cardiac risk and aerobic exercise (AE) training has been described as capable to modulate the HRV. Objective: This study evaluated the temporal effects of aerobic exercise in the HRV in mice exposed to cigarette smoke (CS). Methods: C57Bl/6 mice were divided in 4 groups: Control, Smoke, Exercise and Smoke/Exercise. Smoke groups were exposed to CS for 30min/day (twice), 5days/week for 12 weeks. Exercise groups were trained at moderate intensity for 60min/day, 5days/week for 12 weeks. HRV was measured at baseline and 2, 4, 6, 8, 10 and 12 weeks after the last CS exposure and/or AE session. HRV was measured by cuff (noninvasive tool) applied to the base of the mouse tail connected to PowerLab system. The following parameters were used: heart rate (HR), HRV for time domain (standard deviation of normal beats [SDNN] and root mean square of successive differences in the heart beat interval [RMSSD]) and frequency domain (low frequency [LF], high frequency [HF] and LF/HF ratio). Results: Exposure to CS decreased SDNN and RMSSD values after 6 weeks (p<0.001, compared to control group) where it remained until 10 weeks and AE attenuated this effect. Exposure to CS also decreased HF only after 6 weeks (p<0.01) compared to control group and this effect was reversed to AE training.

864s
Mitochondrial respiration (V'O_2 m) and ROS output before and after inhibition with rotenone (complex-I), malonate (complex-II) and antimycin-A (complex-III) were determined in mitochondria and submitochondrial fragments.

Results: V'O_2 m were 2.8±0.7 vs 7.2±0.5 mmol min^-1 kg^-1 (p<0.001) in COPD vs controls. H_2O_2 outputs by mitochondria oxidizing complex-I substrates were 51.6±130.35 pmol h^-1 mg^-1 (p<0.001) respectively or 0.8% and 2.1% of the V'O_2 m. While antimycin-A greatly increased (<7) H_2O_2 output both in mitochondria and submitochondrial particles in both groups, rotenone only did it in submitochondrial particles. In mitochondria H_2O_2 instead decreased H_2O_2 output as it did malonate, both upstream blockers of the electron flux to complex-III.

Conclusions: Only the ROS generated at complex-III are secreted by the mitochondria. We interpret that this is due to the spatial orientation of complex-I (towards the matrix) and III towards de intermembrane space), being in the first case largely neutralized by the antioxidant system of the mitochondrial matrix.

Iron deficiency as a novel biomarker of functional impairment in patients with chronic obstructive pulmonary disease (COPD)

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Introduction: The role of iron deficiency (IrDe) on exercise intolerance has not been explored in patients with COPD. We hypothesized that IrDe could represent a potentially treatable factor in the functional impairment of COPD patients.

Methods: We evaluated 80 COPD patients (FEV1 1.3±1.5 pred; PaO2 71±11 mmHg; BMI 27±4 kg/m²) recruited at the outpatient consultation office of the Catharina Hospital in Eindhoven, Netherlands. Fe2+ was measured at the Gmelin laboratory index (FeMII) (81±15 vs. 100±6% pred., p<0.01) than those without iron deficiency. Accordingly, IrDe was associated with increased the risk of decreased ET (OR 4: 1.6; IC: 1.48-11.7; p = 0.007), and decreased 6MWD (OR de 3.82; IC: 1.22-8.81; p=0.018).

Results: Forty percent (n=32) of the patients showed IrDe. Iron deficiency did not show association with demographic or pulmonary function variables. But, patients with IrDe showed lower ET (226±25 vs. 362±31 sec, p<0.001), and lower 6MWD (159±119 vs. 209±101 m). In multivariate analysis of sex, age, smoking, and baseline measures of FEVI, RV/TLC-ratio, PatO2 and PaCO2 were analyzed as possible predictors for developing hypoxemia. We used both bivariate and multivariate Cox proportional hazards analyses, with the time from baseline normoxemia until the first event of hypoxemia (PaO2<8kPa) as a measure of event free time. 73 (18%) of the 401 patients were hypoxic at baseline and excluded from the analyses.

Conclusions: Within the three years of follow-up, a total of 46 patients (14%) developed hypoxemia. In bivariate Cox proportional hazards analyses, baseline FeVI, RV/TLC, FFMI, PaO2, and PaCO2 were significantly associated with developing hypoxemia. After multivariate Cox proportional hazards analyses, the following measures remained significantly associated with developing hypoxemia:

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>RV/TLC ratio</td>
<td>1.014 (1.003-1.025)</td>
<td>0.012</td>
</tr>
<tr>
<td>FeO2 (kPa)</td>
<td>0.220 (0.129-0.375)</td>
<td>0.000</td>
</tr>
<tr>
<td>FFMI (k/g)</td>
<td>0.907 (0.830-0.992)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Conclusion: High RV/TLC ratio, low PaO2, and low fat free mass index were predictors for developing hypoxic respiratory failure in a 3 years follow-up of COPD patients.
six-minute walk distance (6MWD) and score were also assessed to determine the BODE index. The average number of sunshine hours was also added.

The number of sunshine hours 2 months before blood sampling was determined using data from the Royal Netherlands Meteorological Institute.

Results: Vitamin D deficient patients had higher RV/TLC, lower pO2, worse 6MWD, higher BODE score and less sunshine hours.

BODE, points 2.2
6MWD, m 316
Modified MRC 0.6

Results:
for haemoglobin concentration.

The data are corrected
by excessive erythrocytosis, severe hypoxemia and occasionally pulmonary hyper-
tension, that may lead to exercise limitation. However, cardiac-pulmonary exercise test (CPET) parameters in this patient group have not been established yet.

Methods: 12 CMS, 14 healthy high- (HH) and 10 lowlanders (LL) were included

Conclusion: Patients with CMS have a preserved aerobic capacity with a ven-
tilatory response identical to LL at sea level but the ventilatory adaptation
decompared to HH and LL at altitude likely explained by preserved oxygen delivery because of increased hemoglobin. This study was supported by a grant from Pfizer.

491. Molecular: pathology of infectious and inflammatory lung disease

P4745
Induced sputum differential gene expression implicates increased p38 signalling activity in severe asthma
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Rationale: There is an urgent need for further insight into the characteristics and classifications of severe asthma. A thorough understanding of the mechanisms underlying the disease processes is essential to this.

Objective: To investigate the mechanisms of severe asthma through differential gene expression and pathways analysis of sputum gene expression profiles.

Methods: Induced sputum was collected from participants with severe asthma (n=13), defined by the presence of poor asthma control (AQLC<1) or airflow ob-
striction (FEV1%predicted<80, FEV1/FVC<70), despite treatment with high-
dose inhaled corticosteroid (>1000μg) and long-acting β2-agonist, and compared to mild and moderate asthma (uncontrolled (n=21)) and controlled (n=21)) and healthy controls (n=13). Gene expression profiles were generated (Illumina HumanMetfall- V2) from sputum RNA and analysed using GeneSpring GX11.

Results: In severe asthma, 1236 genes were altered compared to healthy controls, and 1723 genes were altered compared to healthy controls. Only 48 genes were altered between uncontrolled and controlled asthma. There was enrichment of genes in the p38 signalling pathway associated with severe asthma compared to both controlled asthma and healthy controls. The transformation growth factor-β receptor, interleukin-2 and epidermal growth factor receptor 1 pathways were also enriched in severe asthma when compared to healthy controls.

Conclusions: Severe asthma is associated with substantial differences in sputum gene expression that underlie unique cellular mechanisms that are not just associ-
ated with loss of asthma control. The p38 signalling pathway may be important in the pathogenesis of severe asthma.

P4746
Sputum gene expression of mast cell tryptase and carboxypeptidase A3 are increased in eosinophilic asthma
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Rationale: Little is known regarding the presence and activity of mast cells in the
Objective: To investigate if sputum gene expression of mast cell specific proteins may be associated with asthma inflammatory phenotype.

Methods: Induced sputum was collected from participants with asthma (n=59; eosinophilic n=17; neutrophilic n=12; mixed granulocytic n=12, and paucigranulocytic n=18) and healthy controls (n=17). Gene expression profiles were generated (Illumina Humanel-8 V2) from sputum RNA. Mast cell tryptase (TPSAB1), carboxypeptidase A3 (CTSA) and chymase (CMA1) data were extracted and investigated for their relationship to asthma phenotype.

Results: Gene expression of tryptase and carboxypeptidase A3 was significantly different among the 5 groups (p<0.0001). There was no difference in chymase expression. Tryptase mRNA was increased (p<0.01) in eosinophilic asthma compared to neutrophilic asthma, paucigranulocytic asthma and healthy controls. Carboxypeptidase A3 mRNA was increased (p<0.01) in eosinophilic asthma compared to neutrophilic asthma, mixed granulocytic asthma, paucigranulocytic asthma and healthy controls. Tryptase (r=0.58 p<0.0001) and carboxypeptidase A3 (r=0.59 p<0.0001) expression was strongly correlated with sputum eosinophils.

Conclusions: Gene expression of mast cell tryptase and carboxypeptidase A3 is increased in eosinophilic asthma. Airway mast cells are important in eosinophilic asthma and have a unique phenotype associated with expression of tryptase and carboxypeptidase A3 but not chymase.
TGF-β signaling in non-malignant pulmonary diseases to date is still controversially discussed. Nontypeable Haemophilus influenzae (NTHI) may play a role in the pathogenesis of chronic obstructive pulmonary disease (COPD) as an infectious trigger, but data are available regarding the influence of acute and persistent infection on tissue remodeling and repair factors such as transforming growth factor (TGF)-β. Here we show that the TGF-β pseudoreceptor BAMBI is expressed in the human lung. NTHI infection was analyzed in lungs obtained from COPD patients and controls utilizing a human ex vivo and in vitro models. Detection of NTHI was achieved by in situ hybridization (ISH). For characterization of TGF-β signaling, antibodies were conducted. Expression of the TGF-pseudoreceptor BMP and Activin Membrane-bound Inhibitor (BAMBI) was analyzed using immunohistochemistry (IHC), ISH and RT-PCR. CXC chemokine ligand (CXCL)8, tumour necrosis factor (TNF)-alpha and TGF-β expression were evaluated in lung tissue and cell culture using ELISA.

An infection with NTHI was detected in vivo in 38% of the COPD patients in contrast to 0% of controls. Transcriptome arrays showed no significant changes in TGF-β receptors 1 and 2 and Smad-3 expression, whereas a strong expression of BAMBI with upregulation after in vitro infection of COPD lung tissue was demonstrated. BAMBI was expressed ubiquitously on alveolar macrophages (AM) and epithelial cells interstitial cells (AEC).

We show for the first time a remarkable expression of the TGF-pseudoreceptor BAMBI in the human lung. BAMBI is upregulated in response to NTHI infection in COPD lung tissue in vivo and in vitro.

Elevated osteoprotein in COPD is potentially regulated by oxidative stress
dependent glycosyn synthesis kinase-3β and β-catenin signalling

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We recently reported that spumus osteoprotein (OPG) in COPD is higher than that in controls and is a potential biomarker in COPD (To M et al. CHEST 2010 Dec 2 [Epub ahead of print]). However, the molecular mechanism involved in OPG elevation in COPD was not clarified yet. Here we investigated the role of glycosyn synthesis kinase-3β (GSK-3β) and β-catenin in OPG transcription, especially under oxidative stress.

A549 cells, an alveolar epithelial cell line, were treated with cigarette smoke condensate (CSM), and β-catenin protein was determined by western blot. CSM induced OPG release (measured by ELISA) with a maximum induction of 147% and also increased β-catenin protein expression in a concentration-dependent manner at 24h. A549 cells were transfected with β-catenin siRNA using lipofectamine for specific knockdown (KD) of β-catenin, and IL-1β-stimulated OPG production by the A549 cells was measured by ELISA. β-catenin KD led to lower OPG production when quantified using RT-PCR and western blot. Results: Exposure of 250μg/WT mice to cigarette smoke induced a significant overexpression of HIF-1 mRNA (p>0.03 vs. controls). Likewise, significant VHL mRNA and protein overexpression were elicited (p<0.0006 vs. controls). By contrast, VEGF mRNA expression was not altered (p>0.88).

Conclusion: The current results demonstrate VHL overexpression in skeletal mus-cles of normal mice exposed to CS. This is in analogy and further confirms our recent findings in skeletal muscles of COPD patients. Thus VHL overexpression appears to be an early primary event related to CS exposure rather than a secondary occurrence to development of the COPD pathology.
Adrenergic receptor blocker reverses cardiac metabolic remodeling and improves right ventricular function in experimental pulmonary hypertension

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Albeit right ventricular failure (RVF) is a major complication in patients with pulmonary arterial hypertension, the knowledge on RVF of RVF is still incomplete and RV-targeted therapies are practically non-existent. Since a metabolic switch has been reported for left heart failure, we sought to describe any potential changes in cardiac fuel metabolism and mitochondrial function in RVF. PAH was induced in S-D rats by a combination of a VEGF-receptor blocker followed by 4 weeks of 10% hypoxia. G6PDH Gene expression was evaluated by RT-PCR and confirmed by western blot. T Tests were performed to determine whether spectra of the EXACTLE patients. T Tests were performed to determine whether

Results: Following neutrophil activation or the addition of NE to plasma 325 paired plasma samples from the EXACTLE trial, taken at baseline and following neutrophil activation by ionophore or the addition of neutrophil elastase (NE). 72 paired plasma samples from the EXACTLE trial were subsequently analysed using weak cation exchange beads and Mass spectrometry was used to identify proteolytic fragments in plasma samples. T Tests were performed to determine whether

Methods: As an initial step, we evaluated the expression of PGC1α, a master regulator of mitochondrial biogenesis. Sulfrx RV tissue had a high downregulation of PGC1α when compared to controls (p<0.001). PGC1α target genes were downregulated by fatty acid metabolism. Metabolism were decreased, whereas major glycolysis genes were upregulated. These changes strongly correlated with decreased TAPSE (r=0.77, p<0.001). Furthermore, Sulfrx RV tissue showed a downregulation of TFAM (a critical regulator for mtDNA maintenance) which was associated with abnormal mitochondrial morphology shown by electron microscopy. Carvedilol treatment, a drug known to improve RVF, completely restored

Introduction: Alpha-1-antitrypsin deficiency (ATD) results in an imbalance of proteases and antiproteases with proteolytic destruction of lung parenchyma, and subsequently early onset emphysema. We hypothesised changes in plasma peptides/proteins would be detectable and could provide potential biomarkers to predict a response to treatment in patients with ATD receiving augmentation therapy.

Methods: Mass spectrometry was used to identify proteolytic fragments in plasma following neutrophil activation by ionophore or the addition of neutrophil elastase (NE). 72 paired plasma samples from the EXACTLE trial taken at baseline and 6 months, were subsequently analysed using weak cation exchange beads and MALDI-TOF-MS, to determine whether any of the protein fragments generated in vitro were present in clinical samples and changed significantly in response to augmentation.

Results: Following neutrophil activation or the addition of NE to plasma 325 peptides from 32 proteins were identified. 207 peptide peaks were detected in the spectra of the EXACTLE patients. T Tests were performed to determine whether or not the peak intensities of the peptides changed with treatment. Of these, 12 were significantly different in the treatment group, yet unchanged in the placebo group. The most significant of these had a p value of 2.0E-05.

Conclusion: Changes in the plasma peptides can be found in patient plasma after the addition of calcium ionophore and NE. Some of these changes can be detected in plasma prep/post augmentation. We aim to use more in depth proteomic approaches to further characterise changes in the plasma peptideome, and determine clinical utility as a guide to monitoring and treatment in ATD.

TRP1 expression and characterisation in patients with chronic cough

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Aim: The TRPA1 ion channel is thought to have an important role in the cough reflex. It has been shown that inhalation of cinnamaldehyde, a specific agonist of TRPA1, induces cough in normal human volunteers. We wanted to determine the expression and characterisation of the TRPA1 receptor in human lung tissue.

Methods: Bronchial biopsies were obtained from patients with the Cough Hyper-sensitivity Syndrome on fibre-optic bronchoscopy. Low-resistance samples were obtained from patients undergoing lung resection for lung cancer. Dorsal root ganglia were used as a positive control. These tissue samples were analysed by immunohistochemistry with a specific TRPA1 antibody.

Results: Samples from 14 patients (11 males, mean age 56 years) with the Cough Hypersensitivity Syndrome and 10 lung resection samples (6 males, mean age 68 years) were obtained. All the tissue samples stained for TRPA1. The TRPA1 stain was avidly taken up by the bronchial epithelium, smooth muscle bundles and nerve tissue.

Conclusion: We have described the distribution of TRPA1 ion channel in lung tissue. TRPA1 is agonised by several environmental irritants and endogenous mediators of inflammation. The presence of TRPA1 ion channel in bronchial mucosal nerves and epithelium suggests an important role in the cough reflex. The localisation of these ion channels on smooth muscle could suggest a role in asthmatic inflammation as well.

Expression of the Bcl-2 binding protein beclin 1 in human idiopathic pulmonary fibrosis

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Autophagy is the main cellular route for degradation of long-lived proteins and cytoplasmic organelles and its dysregulation contributes to the pathogenesis of different systemic diseases. In fibroblasts in idiopathic pulmonary fibrosis (IPF) autophagy is decreased, whereas the anti-apoptotic protein Bcl-2 was overexpressed in IPF tissue. The binding of the anti-apoptotic protein Bcl-2 with a key regulator of autophagy Beclin 1 is thought to have an important role in the development of this disease. In some settings it seems to be interconnected with apoptosis. In this regard the binding of the anti-apoptotic protein Bcl-2 with a key regulator of autophagy as Beclin 1 seems to be down-regulated both apoptosis and autophagy. It is known that fibroblasts in idiopathic pulmonary fibrosis (IPF) acquire resistance to apoptosis but no data are available about the regulation of autophagy in IPF. Here we examined the expression of Beclin 1 and Bcl-2 in human IPF fibroblasts before and after cisplatin exposure. We performed immunohistochemistry for Beclin 1 on sections of lung biopsies obtained from patients affected with IPF (n=25) histologically normal (n=5) or with emphysema (n=5). In 4 IPF, 2 normal and 2 emphysema the tissue was used to isolate lung fibroblasts. We performed Western Blot analysis and co-immunoprecipitation for Bcl-2 and Beclin 1 on cultured fibroblasts before and after cisplatin exposure.

Expression of Beclin 1 in fibroblasts from IPF was down-regulated in comparison with normal and emphysema while the anti-apoptotic protein Bcl-2 was over-expressed. Treatment of fibroblast cell cultures with cisplatin induced a significant increase in Beclin 1 but a reduction in Bcl-2 expression in IPF fibroblasts. The immunoprecipitation of Bcl-2 and the following immunodetection of Beclin 1 indicate that Bcl-2 is mainly bound to Beclin 1. The modulated expression of Beclin 1 and Bcl-2 in human IPF fibroblasts in comparison with normal ones seems to suggest the possibility of an autophagic/apoptosis system dysfunction.

B6401

492. Bronchoalveolar lavage and biomarkers in diffuse parenchymal lung disease

Methods: For in vivo inhibition of miR-20a, antagomiR-20a (A-20a) was injected intraperitoneally into mice with hypoxia-induced PH. After three weeks of hypoxia, morphometry and blood gas analysis were performed. RNA levels of miR-20a, BMPR2, Smad5, and Id2 were assessed by real-time PCR in heart and lungs.

Results: Intraperitoneal injection of A-20a resulted in significant down regulation of miR-20a in lungs. When exposed to hypoxia, animals treated with A-20a developed a similar pulmonary hypertrophy induced by relative heart enlargement. Treatment with A-20a reduced the hemoglobin levels and, moreover, the acid-base status (base deficit) approached the baseline values of normoxic animals. Molecular analysis showed down regulation of BMPR2 mRNA levels in lung tissue by hypoxia (0.79±0.24 fold, p=0.039). A-20a abrogated the hypoxia induced down regulation of BMPR2 and led to significant up regulation of BMPR2 (1.62±0.18 fold, p<0.001). We detected increased expression of Smad5 (1.29±0.19 fold, p=0.003) and the BMP target gene Id2 (1.43±0.40 fold, p=0.02) in lung tissue of A-20a treated mice suggesting improved BMP signaling.

Conclusion: Our data underpin the importance of miR-20a in the BMP signaling and emphasize the need for further studies to address the therapeutic potential of antagonismRs for the human disease.

Plasma protein profiling in alpha-1-antitrypsin deficiency

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Overexpression of matrix metalloproteinase-7 (MMP-7) in bronchoalveolar lavage fluid (BALF) of IPF and lung cancer patients

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It is long recognised that lung cancer has an increased frequency in idiopathic pulmonary fibrosis and is associated with abnormal mitochondrial morphology shown by electron microscopy. Carvedilol treatment, a drug known to improve RVF, completely restored
pulmonary fibrosis (IPF), raising questions regarding the similarity of IPF and lung cancer biology. Matrix metalloproteinases regulate remodelling of the extracellular matrix, an important function for pathological processes such as angiogenesis, tissue repair and tumor invasion. Our aim is to assess the expression of this pathway in BALF samples of lung cancer patients and compare with IPF patients to examine possible pathogenetic links between these two lethal pulmonary diseases.

We prospectively studied 23 newly diagnosed patients, with non small cell lung cancer (NSCLC), 10 IPF patients and 10 healthy controls (C). MMP2, MMP7, MMP9, TIMP1 and TIMP2 mRNA expression levels were measured in BALF by real time RT-PCR. MMP7 protein levels were measured in BALF supernatants using ELISA kit.

mRNA expression of MMPs 2, 7, 9 and TIMP1 was significantly increased in lung cancer compared to controls (p<0.05). The IPF population showed decreased expression of the aforementioned MMPs in comparison with lung cancer while did not show significant difference at the mRNA level in comparison to controls. MMP7 protein levels (pg/ml) were significantly higher in both NSCLC and IPF populations compared to controls (NSCLC: 24.69±4.18, IPF: 18.85±2.11, C=9.76±1.92, with p values: NSCLC vs C p=0.032, IPF vs C p=0.005).

Increased expression of MMP-7 in both m-RNA and protein level may suggest a common mechanism between lethal disorders. Given that our populations were not matched, the over-expression of these markers could be predictive of tumor progression, migratory behaviour and metastasis potential.

P4762
Expression profiling of Th17 cell activators revealed elevation of STAT-3 in progressing sarcoidosis
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Sarcoidosis is a Th1/Th17 multisystem inflammatory disorder of unknown aetiology. Although Th17 cells have been implicated in sarcoidosis and its progression, there is limited information about the molecules involved in the Th17 immune response in sarcoidosis and its phenotypes.

We, therefore, investigated mRNA expression of Th17 pathway activators (IL-6, IL-21, IL-23, TGFbeta, RORC) in BAL cells irrespective of clinical phenotype. Enhanced expression of STAT-3, an essential regulator of Th17 cells, was detected in progressing sarcoidosis (p<0.0001). Expression of STAT-3 was significantly higher in both NSCLC and IPF groups compared to controls (NSCLC: 24.69±4.18, IPF: 18.85±2.11, C=9.76±1.92, with p values: NSCLC vs C p=0.032, IPF vs C p=0.005).

In conclusion, increased expression of Th17 activators (IL-6, IL-21, IL-23, TGFbeta, RORC) was observed in sarcoid BAL cells irrespective of clinical phenotype. Increased expression of Th17 activators (IL-6, IL-21, IL-23, TGFbeta, RORC) was observed in sarcoid BAL cells irrespective of clinical phenotype.

P4764
Characterization of myofibroblasts cultured from small volumes of diagnostic bronchoalveolar lavage fluid samples
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Myofibroblasts are supposed to have a key role in pathogenesis of fibrotic lung diseases. Our aim was to standardize process for culturing cells from small volumes of diagnostic bronchoalveolar lavage (BAL) fluid samples and to characterize the cultured cells. Small volumes of BAL samples were collected from 98 patients that underwent bronchoscopy and BAL for diagnostic purposes. Cells were visualized by electron and immunoelectron microscopy. Proliferation and invasion capacities as well as stem cell properties of the cells were evaluated. Colonies of proliferating fibroblast type cells could be seen in 62% of samples. The success rate varied significantly based on the disease being 92% in idiopathic pulmonary fibrosis (IPF), 80% in non-specific interstitial pneumonia, 80% in collagen vascular disease associated interstitial lung disease, 62% in asbestosis, 55% in sarcoidosis, 100% in allergic alveolitis, 80% in drug reaction, 40% in lung cancer and 25% in normal lung. The success was not dependent on volume or cell amount of the BAL sample. The cultured cells were either fibroblasts or myofibroblasts. Typical features of myofibroblasts were detectable in the cells by electron and immunoelectron microscopy. Some cell samples exhibited differentiation potency into osteoblasts or adipocytes. The invasion capacity varied in different disorders. Myofibroblasts could be cultured from small volumes of diagnostic BAL fluid samples. This method could increase the usability of BAL fluid both in diagnostics of interstitial lung diseases and in scientific research.

P4765
Mechanisms of impaired immune surveillance in lower airways of smokers.

Data from bronchoalveolar lavage (BAL) harvested in selected interstitial lung diseases (ILDs) and control group

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Background: Cigarette smoke is recognized as a cause of lung tumors, due to its carcinogenic potential. Less is known about suppressed local immune surveillance.

Methods: Alveolar lymphocytes (AL) were obtained by bronchoalveolar lavage (BAL) in pulmonary sarcoidosis (PS), idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP) and control group (C) by BAL. The cultured cells were either fibroblasts or myofibroblasts. Typical features of myofibroblasts were detectable in the cells by electron and immunoelectron microscopy. Some cell samples exhibited differentiation potency into osteoblasts or adipocytes. The invasion capacity varied in different disorders. Myofibroblasts could be cultured from small volumes of diagnostic BAL fluid samples. This method could increase the usability of BAL fluid both in diagnostics of interstitial lung diseases and in scientific research.

Conclusions: The decreased immune surveillance in smokers lower airways include higher AL apoptosis rate and increased AL susceptibility to TGFβ. The decreased immune surveillance in lower airways of smokers.

Results: AL apoptosis rate was reduced in PS (0.7±0.2%, p<0.05) and increased in IPF (2.3±1.0%, p<0.05) as compared to nonsmokers. IFNγ levels were lower in all smoking subgroups than in respective nonsmokers. No changes were found in TNFα and TNF levels, but AL expression of TGFβ1 and TNF (CD105a) receptors was higher in smoker subgroups (significant for CD105a in IPF and CD102a in PS).

Conclusions: The decreased immune surveillance in smokers lower airways include higher AL apoptosis rate and increased AL susceptibility to TGFβ. The decreased immune surveillance in lower airways of smokers.
P4766
Expression of transforming growth factor β (TGFβ) receptor, CD105, is declined in Th1 interstitial lung diseases (ILDs)

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Background: TGFβ, as the most potent activator of lung fibrosis, stimulates fibroblast proliferation and induces secretion of collagen and other extracellular matrix proteins. It reveals its profibrotic effect by receptor complex, including CD105 molecule.

Methods: TGFβ levels was examined by ELISA in bronchoalveolar lavage (BAL) supernatants. CD105 expression was tested on BAL macrophages and lymphocytes in pulmonary sarcoidosis, (n=16), idiopathic pulmonary fibrosis (IPF, n=9), non-specific interstitial pneumonia (NSIP, n=6) and extrinsic allergic alveolitis (EAA, n=7). CD105 appearance was also assessed in model lung cell lines: pneumocytes type 2 (A549) and fibroblasts (HLF-1).

Results: IF was the only disorder with significantly increased TGFβ level. CD105 expression is common on HLF-1 (98%), A549 (63%, median of 5 trials) and alveolar macrophages. In PS significantly decreased CD105 expression on BAL lymphocytes was found (all lymphocytes: 7.2±0.6%, Th cells: 4.6±0.4%, Tc cells: 1.8±0.3%, resp. control values: 13.3±4.3, 6.6±2.6% and 4.7±1.1%, median±SEM, p<0.05). Similar results were observed in EAA. IF was characterized by remarkably enhanced BAL CD105 lymphocyte percentage (all lymphocytes: 23.9±5.8%, p<0.05).

Conclusions: TGFβ receptor, CD105, is frequently present in lower airways. Lower BAL CD105+ lymphocyte percentage in IF, and higher one in PS and EAA may reflect different Th1/Th2 polarization pattern. Summarizing, the key role of diverse lower airway cell reactivity to TGFβ in ILDs should be considered.

P4767
Proteological assessment of idiopathic pulmonary fibrosis and hypersensitivity pneumonitis by means of broncho-alveolar lavage

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Background: The diagnostic strategy of the drug-induced lung disease (DILD) has not been established. It remains to be determined whether the lymphocyte transformation test (LTT) can be used for the diagnosis of DILD. Although bronchoalveolar lavage (BAL) is often performed, its usefulness in the diagnosis of DILD is still uncertain.

Introduction and aims: We aimed to evaluate the diagnostic values of BAL and LTT in patients with DILD.

Method: We retrospectively analyzed 47 patients who were suspected as DILD and underwent BAL and LTT between January 2004 and September 2009. The total cell number and the differential count of leukocytes in BAL fluid were determined. The levels of cytokines (eotaxin-1, -2, -3, and RANTES) in the supernatant were measured by ELISA. It was also evaluated whether these parameters were useful for the diagnosis of DILD.

Results: The diagnostic sensitivity and specificity of LTT were 50% and 60%, respectively. These numbers were comparable to those in previous reports. The diagnostic value of LTT in IPF was 90%, and the specificity was 22%. The sensitivity of increased eosinophils (>5%) in BAL fluid was 90%, and the specificity was 22%. These numbers were comparable to those in previous reports. The diagnostic sensitivity and specificity of LTT were 50% and 60%, respectively. These numbers were comparable to those in previous reports. The diagnostic value of LTT in IPF was 90%, and the specificity was 22%

Conclusions: We speculated that BAL fluid findings, especially the differential count of leukocytes, may be useful for the diagnosis and the prediction of outcome of the patients with DILD.

P4769
Clinical and functional features in idiopathic pulmonary fibrosis (IPF) with and without haemosiderin-laden alveolar macrophages on BALF

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We have previously reported increased frequency of haemosiderin-laden alveolar macrophages in patients with IPF. We performed a retrospective analysis of 49 patients who received diagnosis of IPF. The diagnostic value of IF was in agreement with the ATS/EERS guidelines. BALF was performed in all subjects. We evaluated the occurrence of haemosiderin-laden alveolar macrophages in patients with IF.P. Patients with a history of smoking were excluded. BALF was performed in all subjects and underwent BAL and LTT between January 2004 and September 2009. The total cell number and the differential count of leukocytes in BAL fluid were determined. The levels of cytokines (eotaxin-1, -2, -3, and RANTES) in the supernatant were measured by ELISA. It was also evaluated whether these parameters were useful for the diagnosis of DILD.

Results: The diagnostic sensitivity and specificity of LTT were 50% and 60%, respectively. These numbers were comparable to those in previous reports. The diagnostic value of LTT in IPF was 90%, and the specificity was 22%

Conclusions: We speculated that BAL fluid findings, especially the differential count of leukocytes, may be useful for the diagnosis and the prediction of outcome of the patients with DILD.

P4770
Differential cell count in BAL by flow cytometry using CD15

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Introduction: Usually inflammatory cell counts in bronchoalveolar lavage (BAL) are done manually on optical microscopy (OM) despite the high intra- and interobserver variability. The object was to compare inflammatory cell counts performed by OM with these counts by flow cytometry (FC) with a new combination of monoclonal antibodies.

Conclusion: Differences for aforementioned mechanisms were observed in IF and HP compared to control, as well as discriminating factors between IF and HP. These results highlight the role of BAL in the search for new biomarkers and therapies for pulmonary fibrosis.
Methods: 34 BAL samples were analysed in a 2-laser cytometer (FACS Calibur). The results were compared with those obtained by optical microscopy. The proposed combination of monoclonal antibodies identified two leukocyte subsets as CD45+ cells and lymphocytes as CD16−, CD14+ (NK lymphocytes), HLA-DR− and HLA-DR+ (B cells and activated lymphocytes) cells; neutrophils as CD15+CD66b−, CD16+CD66b−, HLA-DR− cells; eosinophils as CD15+CD66b−, CD16−, HLA-DR− cells and alveolar macrophages as CD14+CD16−. Macrophages' autofluorescence (AF) was overcome using the monoclonal antibody anti-HLA-DR conjugated with the dye APC as the main identification marker. Results: Flow cytometry showed high correlations (r=0.70 to 0.93; p<0.001) but FCM overestimates lymphocyte population +13 (15.6%), and conversely underestimates alveolar macrophage population −15.9 (16.6%). Conclusions: The monoclonal antibodies combination proposed is effective and reliable to identify leukocyte populations in BAL. The process is simpler and faster than manual optical microscopy but some differences in macrophages and lymphocytes counts should be considered.

P4771

LSC 2011 Abstract: Bronchoalveolar lavage in radiation pneumonitis after radiotherapy for breast cancer
Claudia Lucia Toma, Aneta Serbescu, Mihai Alexe, Luminita Cervis, Diana Ionita, Miron Alexandru Bogdan. Pneumonology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2Pneumonology, Marius Nasta Institute of Pneumonology, Bucharest, Romania

Radiotherapy pneumonitis is a complication of radiotherapy which limits its application in cancer therapy. Aim: To compare the bronchoalveolar lavage (BAL) findings in patients with symptomatic radiation pneumonitis (RP) versus asymptomatic patients and healthy controls. Material and method: We evaluated 65 female patients with RP after radiotherapy for breast cancer.

Results: Forty-nine patients were symptomatic (fever, cough and/or dyspnea) and 16 were asymptomatic. All patients had a newly discovered infiltrate or ground-glass opacities in chest radiography, corresponding to the radiation field. BAL in symptomatic patients had an increased number of cells.

Lymphocytosis was present in all patients with RP, but it was higher in symptomatic patients (34.9±18.81% vs. 26.14±14.3%). Macrophages were decreased in all patients. Neutrophils were slightly increased (8.88% in symptomatic and 3.34% in asymptomatic) and eosinophils were normal in both groups (2.56% and 1.22, respectively). Almost all lymphocytes were T type (CD3+). CD4+ lymphocytes were increased in both groups with normal CD4/CD8 ratio (2.72 in symptomatic and 1.5 in asymptomatic group).

Conclusions: Lymphocytic alveolitis with T lymphocytes was present in all patients with RP with a higher proportion in symptomatic patients.

P4772

Detection of differences in volatile organic compounds (VOCs) by ion mobility spectrometry (IMS) of exhaled breath in patients with interstitial lung diseases (ILDs) compared to healthy controls (HC)
Olaf Anhenn, Thomas Rabis, Lurc Rad, Gerhard Weinreich, Helmut Teschler, Ulrich Costabel.

Aim and objective: To compare the bronchoalveolar lavage (BAL) findings in patients with symptomatic radiation pneumonitis (RP) versus asymptomatic patients and healthy controls. Material and method: We evaluated 65 female patients with RP after radiotherapy for breast cancer.

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Conclusions: Lymphocytic alveolitis with T lymphocytes was present in all patients with RP with a higher proportion in symptomatic patients.

P4774

Serum napsin A is a novel diagnostic and monitoring marker for interstitial lung disease
Takuya Yamakawa, Tsumoto Hamada, Kousuke Inoue. Department of Pulmonary Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

Background: Idiopathic Pulmonary Fibrosis (IPF) is a progressive, fatal lung disease of unknown etiology still lacking of effective therapy. IPF has a poor prognosis with a median survival of 2.5-3.5 years, and it is associated with lung cancer with a prevalence ranging from 4.8% to 46%. Molecular mechanisms of carcinogenesis occurring in IPF remain to be clarified.

Aim and objective: The family of emrin/adrinin/moerin (ERM) proteins is essential for maintenance of cell shape, cell adhesion, migration and division, serving as an important cross-linker between the plasma membrane and cytoskeleton. Recent studies showed that ERM is upregulated in multiple types of metastatic cancers. In the current investigation, we tested the hypothesis that ERM interacts and phosphorylates in a key role in epithelial-mesenchymal transition (EMT) in alveolar epithelial cells.

Methods: In order to identify the relationship between lung cancer and IPF we assessed an immunohistochemistry analysis for phospho-ERM in the following pulmonary biopsy specimens: 20 IPF/1 UIP, 4 adenocarcinoma, 6 cryptogenic organizing pneumonia (COP), and 4 normal controls.

Results: Our preliminary data showed in normal lung samples a totally negative phospho-ERM immunostaining. We found a weak positivity in COP samples, whereas in UIP samples we found a higher global expression, in particular in activated type II pneumocytes and basal bronchiolar cells.

Conclusion: We hypothesize that activation of ERM proteins could be involved in UIP pathogenesis, leading to possible contribution to the EMT process of lung epithelial cells.

P4775

Extracellular matrix profile of lung in idiopathic pulmonary fibrosis
Susanna Estany, Vanesa Vicens, Roger Llatjós, Rosa Pené, Ignacio Escobar, Antonia Xaubet, Federic Mamresas, Jordi Dorca, Maria Molina-Molina.

Aim and objective: To compare the bronchoalveolar lavage (BAL) findings in patients with symptomatic radiation pneumonitis (RP) versus asymptomatic patients and healthy controls. Material and method: We evaluated 65 female patients with RP after radiotherapy for breast cancer.

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Conclusions: Lymphocytic alveolitis with T lymphocytes was present in all patients with RP with a higher proportion in symptomatic patients.
P4776 Elevation of serum tumor markers in patients with interstitial lung disease Jiquan Liu1, Haoping Dai1, Longkai Liang1, Liying Peng1, Jing Yang2,1Respiratory Medicine, Beijing Chaoyang Hospital; 2Department of Capital Medical University; Beijing Institute of Respiratory Medicine, Beijing, China.

The risk of lung cancer is high in patients with interstitial lung disease (ILD). It was reported that tumor markers was increased in ILD patients. The serum levels of CEA, CA19-9, CA125 andNSE were measured in 58 ILD combines lung cancer (ILD-CA) patients, 632 ILD patients and 632 control subjects. The analysis of covariance, multiple linear regression, Logistic regression analysis and analysis of variance were used for statistical analyses. The serum levels of CEA, CA19-9, CA125 and NSE were higher in ILD-CA patients than the control group (P<0.01). They were higher in patients with ILD-CA than those in patients with ILD and control (P<0.05). The levels of CEA and CA125 in ILD group were higher than the control group (P<0.01). The ILD group included idiopathic pulmonary fibrosis (IPF) subgroup of 214 cases, non-IPF idiopathic interstitial pulmonary (non-IPF-ILD) subgroup of 97 patients, collagen vascular disease associated ILD (CVD-ILD) subgroup of 163 cases, and other ILD subgroup of 158 cases. The serum levels of CEA, CA19-9 and CA125 were the highest in patients with IPF than the other three subgroups of ILD (P<0.01). Adjusting the confounding factors such as gender, age and smoking condition, the risk of CVD-ILD increased with the elevation of CEA and CA125. This study provides that the elevation of serum tumor markers in patients with ILD-CA is a common sign, and is also an important sign in patients with ILD, especially in patients with IPF. Incidence of lung cancer is increased in ILD patients with elevation of the serum levels of CEA and CA125.

P4777 Interferon-γ or azathioprine plus corticosteroids do not alter the expression of apoptotic markers in alveolar macrophages of patients with IPF Fotios Drakopoulos1, Ateni Xyteri1, Evangelos Tsiambas1, Fotios Drakopoulos1, Atenis Xyteri1, Evangelos Tsiambas1,2

Aim: To examine the expression of apoptotic proteins in AM of patients with IPF after therapeutic intervention.

Methods: Twenty newly diagnosed IPF patients were randomised in Group A treated by a combination of interferon-γ1b and prednisolone and group B treated by azathioprine and prednisolone. Groups were compared regarding clinical deterioration, lung function, and bronchoalveolar lavage (BAL) apoptosis markers. We analyzed by immunohistochemistry, the expression of the anti-apoptotic markers bcl-2 and the pro-apoptotic markers bax, fas, fag ligand in AM obtained from BAL before and after treatment. We measured apoptosis by TUNEL.

Results: No difference was observed regarding age, gender, smoking habit between the two groups of IPF patients. The patients of both groups had similar FEV1, FVC and DLCO values at entry and after six months of treatment. We found no difference in the expression of apoptotic markers in AMs before and after treatment between groups. We found no correlation between clinical and functional parameters and change in apoptotic markers.

Conclusions: We specifically examined the expression of apoptotic markers in AMs of patients with IPF and we report that different treatment options do not affect the expression of these markers in IPF. These results may be related to the ineffectiveness of pharmacological therapies for IPF.

P4778 Reliability of ATS/ERS criteria for the diagnosis of idiopathic pulmonary fibrosis Shinichiro Ohshima1,2, Francesco Bonella1, Koichi Tanigawa2, Nobukiyo Kehno3, Jousue Guzman4, Ulrich Costabel1, 1Department of Pneumology/Allergy, Ruhrlandklinik, University Hospital, Essen, Germany; 2Department of Emergency and Critical Care Medicine, Hiroshima University, Hiroshima, Japan; 3Department of Molecular and Internal Medicine, Hiroshima University, Hiroshima, Japan; 4General and Experimental Pathology, Ruhr-University Bochum, Bochum, Germany.

Background: The 2002 ATS/ERS Consensus Classification has been widely accepted as the standard classification for interstitial lung diseases (ILD). However, the diagnostic accuracy of the major/minor criteria in the ATS/ERS Classification for idiopathic pulmonary fibrosis (IPF) is still controversial.

Aims and objectives: To evaluate the reliability of the major/minor criteria in the ATS/ERS Classification for IPF.

Methods: Patients with ILD admitted to Ruhrlandklinik (Essen, Germany) were retrospectively studied. All patients presenting with an insidious onset and a duration of illness >3 months were included. Because of the concept that the exclusion of known causes for ILD is not always easy, we also enrolled patients with secondary ILD (dust/drug exposure or CVD-associated). The diagnostic accuracy of the major/minor criteria for IPF was estimated.

Results: A total of 163 patients with suspected ILD were studied. The final diagnoses of the enrolled patients were IPF (n=82), other IIP (n=42) and secondary ILD (n=39). In the univariate analysis, the p-value of the criteria (%VC<80%,%TLC<80%,%DLCO<80%, A-aDO2>35mmHg, PaO2<60mmHg, typical findings for IPF in HRCT, BAL lymphocytosis <30% age, 50, and bibasilar crackles) for the diagnosis of IPF were 0.04, 0.94, 0.65, 0.08, 0.29, <0.0001, 0.0001, 0.0001, 0.97, and 0.0015, respectively. In the multivariate analysis, the typical findings for IPF on HRCT and BAL lymphocytosis <30% (p=0.0001) showed significant diagnostic significance for IPF.

Conclusions: Typical findings for IPF in HRCT and BAL lymphocytosis <30% were of diagnostic significance for IPF.
Background: Nasal nitric oxide (n-NO) has been suggested as a screening test for primary ciliary dyskinesia (PCD) as patients with PCD have lower n-NO levels than healthy controls. Recent studies on n-NO in PCD and secondary ciliary dyskinesia (SCD) show an overlap between these two groups.

Methods: n-NO was measured in duplicate by aspiration at 5 mL/s with NBOX 5 (Novo Nordisk, Denmark) in 21 patients with clinical diagnosis of PCD (7 male, 14 female, age 14.8 ± 10.2 years) and 20 healthy control subjects (7 male, 13 female, age 15.1 ± 11 years). The control group was recruited from healthy individuals consuming a normal diet in the hospital cafeteria or employees of the hospital. The use of asthma medications, respiratory infections, and nasal allergy medications were recorded.

Results: n-NO levels were significantly lower in the PCD group than in healthy controls (4.4 ± 2.2 ppb vs 2.6 ± 1.9 ppb, p=0.006). Both bronchial (p=0.0016) and alveolar FENO (p=0.017) were positively correlated with Crohn’s Disease Activity Index (CDAI).

Conclusions: Our results for bronchial and alveolar FENO confirm subclinical pulmonary involvement in Crohn’s disease. FENO may be of clinical value during follow-up of these patients as a surrogate marker of systemic inflammation.

P4782 Can nasal-NO be used to differentiate between primary and secondary ciliary dyskinesia? 
Christina Krantz1, Andrei Malinovischii2, Annika Hollings1, Kjell Alving1, 2
1Women and Children’s Health, Uppsala University Hospital, Uppsala, Sweden; 2Medical Sciences, Clinical Physiology, Uppsala University Hospital, Uppsala, Sweden

Background: Nasal nitric oxide (n-NO) has been suggested as a screening test for primary ciliary dyskinesia (PCD) as patients with PCD have lower n-NO levels than healthy controls. Recent studies on n-NO in PCD and secondary ciliary dyskinesia (SCD) show an overlap between these two groups.

Methods: n-NO was measured in duplicate by aspiration at 5 mL/s with NBOX 5 (Novo Nordisk, Denmark) in 21 patients with clinical diagnosis of PCD (7 male, 14 female, age 14.8 ± 10.2 years) and 20 healthy control subjects (7 male, 13 female, age 15.1 ± 11 years). The control group was recruited from healthy individuals consuming a normal diet in the hospital cafeteria or employees of the hospital. The use of asthma medications, respiratory infections, and nasal allergy medications were recorded.

Results: n-NO levels were significantly lower in the PCD group than in healthy controls (4.4 ± 2.2 ppb vs 2.6 ± 1.9 ppb, p=0.006). Both bronchial (p=0.0016) and alveolar FENO (p=0.017) were positively correlated with Crohn’s Disease Activity Index (CDAI).

Conclusions: Our results for bronchial and alveolar FENO confirm subclinical pulmonary involvement in Crohn’s disease. FENO may be of clinical value during follow-up of these patients as a surrogate marker of systemic inflammation.
EBT was recorded with a breath thermometer (X-Halo, Delmedica Investments Ltd, Singapore), spirometry was done, patients completed the COPD Assessment Test (CAT) and the first spontaneous sputum in the morning was collected and processed (Yamamoto C et al. Chest 1997). Paired t-test and Spearman correlation were used.

**Results:** EBT at exacerbation was higher compared to that at recovery (34.42±0.73°C vs. 34.03±0.50°C, p<0.03). Sputum neutrophil percentage at exacerbation showed a positive correlation with EBT (r=0.78, p<0.02), and fell after treatment (57.12% vs. 39.1±18%, p<0.04). EBT at exacerbation was not related to spirometric variables or CAT score.

**Conclusion:** EBT rises at acute exacerbation of COPD and it is associated with increased airway inflammation. Measuring exhaled breath temperature might be useful for monitoring airway inflammation in COPD.

The study was supported by Hungarian Respiratory Society grants (to Zsófia Lázár) and OTKA 68808.

**P4785**

Neutrophilic airways inflammation in lung cancer: The role of exhaled LTB-4 and IL-8

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Recent advances in lung cancer biology presuppose its inflammatory origin. In this regard, LTB-4 and IL-8 are known to play a crucial role in neutrophil recruitment into airways during lung cancer.

Notwithstanding the intriguing hypothesis, the exact role of neutrophilic inflammation in tumor biology remain complex and not completely known.

The aim of this study was to give our contribution in this field by investigating LTB-4 and IL-8 in the breath condensate of NSCLC patients and verifying their role in cancer development and progression.

We enrolled 30 NSCLC patients and 25 controls. LTB-4 and IL-8 concentrations were measured in the breath condensate and the blood of all the subjects under study using ELIA kits. Thirty NSCLC patients and ten controls underwent induced sputum collection and analysis.

LTB-4 and IL-8 resulted higher in breath condensate and the blood of NSCLC patients compared to controls. Significantly higher concentrations were found as the cancer stages progressed. A positive correlation was observed between exhaled IL-8 and LTB-4 and the percentage of neutrophils in the induced sputum.

**Conclusion:** The high concentrations of exhaled LTB-4 and IL-8 showed the presence of a neutrophilic inflammation in the airways of NSCLC patients. The treatment of acute exacerbations is of major importance since they have a given impact on the morbidity, mortality and health care costs associated with COPD.

**Objective:** It is well known that the airway inflammation is enhanced at exacerbation. The purpose of this study is to investigate if the volatile organic compounds (VOCs) detected in the exhaled breath of patients with an acute exacerbation of COPD are different from those detected in patients with a stable disease.

**Methods:** Breath samples were collected via a side-stream Teflon tube and measured directly by an ion mobility spectrometer coupled to a multi capillary column (MCC/IMS). VOCs were detected and statistically evaluated in order to discriminate COPD patients with an exacerbation from those with a stable disease.

**Results:** Thirteen COPD patients with an acute exacerbation, 46 COPD patients with a stable disease as well as 51 healthy subjects were included in the study.

Several peaks were found to differentiate in the group of patients with an acute exacerbation compared to the COPD patients with stable disease and with healthy subjects.

**Conclusion:** Our data suggest that specific VOCs can be detected in the exhaled breath of COPD patients with an acute exacerbation indicating possibly the enhanced airway inflammation. The identification of VOCs that characterise the acute exacerbations could be used as diagnostic tool for an exacerbation apart from the clinical criteria.

**P4787**

Targeted eicosanoid lipidomics of induced sputum as compared to exhaled breath condensate in asthmatics

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Eicosanoids are mediators of arachidonic acid pathway. Induced sputum (IS) is a non-invasive material from the lower airways, its sampling is well standardized. Advantage of exhaled breath condensate (EBC) is shorter collection time and low protein content, this is compromised by extreme dilution and inter-individual variation. Both matrices have been introduced for assessment of inflammatory mediators in asthma.

We compared eicosanoids concentration in IS and EBC samples collected according to the current guidelines and estimated redistribution of eicosanoids and their metabolites as a result of sample processing.

EBC was collected from asthmatics using Jaeger ECO Screen I; IS according to the most recent ERS Task Force recommendations. The same validated quantitation mass spectrometry was used for both matrices eicosanoids’ measurements. Random IS samples were split to test enzymatic inhibition during solubilisation. We quantified 29 eicosanoids, including major prostaglandins, leukotrienes, and their metabolites. Average concentration of eicosanoids was 82±[400] times lower in EBC than in IS. IS differed form EBC by higher HETE and undetectable LTC4. Conversion of LTB4 into 5-oxo-LTB4 and increase of tetranor-PGEM was observed during IS solubilisation, non-physiological pH prevented these redistributions only partially.

Although processing of IS shifts eicosanoid profile toward metabolites, significant amounts of mediators are present within detection levels of common immunosays. A strict adherence to the IS collection protocols is recommended to avoid a pre-analytical bias.

In collaboration with U-BIOPRED within the Innovative Medicine Initiative.
**P4790**

**Detection of pseudomonas aeruginosa (Pa) specific peaks by ion mobility spectrometry (IMS) in exhaled breath of bronchiectasis patients**

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**Introduction:** Colonisation or infection of airways from bronchiectasis patients by *Pa* results in chronic inflammation leading to a progressive destruction of the lung and to a decline in lung function. Therefore, more urgent stays for intravenous antibiotic treatment are necessary and the quality of life in these patients is severely limited.

**Objectives:** Aim of our study was to detect and compare volatile organic compounds (VOCs) by IMS in exhaled breath of bronchiectasis patients either colonised or infected by *Pa* with healthy non-smoking controls (hc).

**Methods:** We have analysed VOCs by IMS coupled to a multi-capillary column (MCC) for pre-separation (MCC-IMS) and Analysitk in exhaled breath of bronchiectasis patients either colonised or infected by *Pa* with healthy non-smoking controls (hc).

**Results:** Using IMS for VOC analysis, differences between Pa+ and hc could be found. Different peaks were detected between Pa+ and hc, Pa+ and the samples from asthma patients (Pa-c) as well as Pa+ and Pa-c. VOC analysis from Pa cultures revealed two peaks which could be found in the Pa+ bronchiectasis patients.

**Conclusions:** IMS seems to be a promising method for the non-invasive identification of patients which are colonized or infected with *Pa*. A differentiation between patients with *Pa* colonised or infected with Pa is possible, as well. However confirmation of our findings in a larger study population is needed. The comparison of Pa+ with Pa-c cultures will help to identify peaks caused by the presence of Pa.

**Furthermore, it is required to identify the molecules representing the peaks.**

**P4791**

**Metabolomic analysis of exhaled breath condensate in diagnostics of obstructive airway diseases**


**Faculty of Mechanics and Mathematics, M.V. Lomonosov Moscow State University, Moscow, Russian Federation**

**Introduction:** Metabolomic analysis provides molecular and biochemical profiles of metabolites in different biological fluids.

**Objectives:** The aim of this study was to assess the potential of exhaled breath condensate (EBC) molecular profiling in discrimination patients with COPD and asthma and healthy subjects.

**Methods:** Twenty patients with asthma, twenty patients with COPD and thirty healthy control subjects were enrolled in cross-sectional study. Every subject performed spirometry and EBC collection. EBC samples were analyzed by gas chromatography – mass-spectrometry method (GC-MS). EBC profiles from patients with asthma were separated from patients with COPD and from healthy control subjects using an algorithm based on linear methods of pattern recognition theory.

**Results:** We have detected various profiles of semi-volatile organic compounds (SVOC) in EBC in patients with COPD, asthma and healthy subjects. Mathematical approach to available data revealed 9 SVOC which have been deemed the most appropriate for solving recognition problem (2-phenoxethanol, decanol-1, ethyl 2,3-dihydro-1H-inden-1-ol and others). EBC profiles of healthy subjects can be distinguished from patients with asthma with reliability 75%, healthy subjects from COPD patients with reliability 85% and asthma patients from COPD patients with reliability 83%.

**Conclusion:** Metabolomic analysis of EBC can discriminate patients with asthma and COPD and healthy subjects. We propose that differences in SVOC profiles between asthma and COPD are disease related.

**P4792**

**Discrimination of protein and peptide composition of exhaled breath condensate in patients with pulmonary disease by mass spectrometry**

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**Objective:** Exhaled breath condensate (EBC) reflects the composition of the airway-lining fluid and may contain biomarkers of diseases of respiratory system.

**Methods:** For the study of exhaled breath condensate (EBC) of patients with obstructive pulmonary disease (COPD) and pneumonia we used 2D-PAGE and MS analysis. Peptides derived from bronchoalveolar lavage fluid (BALF) of 10 COPD (8 M, age 63.3 ± 7.9) were evaluated at baseline (T0) and after 12 weeks (T1) of oral administration of a curcumin based herbal preparation (Curostal®) and compared to healthy non-smoking controls (hc). 876s

Among clinical parameters BSCN score was 4.9±1.0 at T0 and 7.5±1.0 at T1, while FEV1 values resulted slightly but not significantly increased at T1. Conclusions: NMR metabolomic is a sensitive method to explore nutritectic effects of exogenous antioxidant on EBC in patients affected by COPD.

**P4793**

**NMR EBC metabonomics to assess the nutritectic effect in COPD. A pilot study of oral administration of a curcumin based herbal preparation**

Guglielmo de Laurentis1,2, Giovanni Scapagnini1, Deborah Paris3, Dominique Melch3, Mauro Maniscalco1, Andrea Motta1, Sofia Mattos1, Andrea Bianco1, 1Dept. of Respiratory Medicine, University “Federico II” of Naples, Naples, Italy; 2Dept. of Health Sciences, University of Molise, Campobasso, Italy; 3Institute of Molecular Chemistry, National Research Council, Pescocostanzo, Italy; 4Dept. of Medicine, Rehabilitation Center, Santa Maria del Pozzo, Summa Vesuviana, Italy

**Background:** NMR metabolomic of EBC significantly divide healthy from COPD patients, identifying specific profiles linked to cellular oxidative pattern. Curcumin is a recognized anti-oxidant agent in biochemical cellular balance. As it is still unknown of the pattern recognized by NMR metabolomic spectroscopy in COPD is sensitive to exogenous nutrients, in this preliminary open label study we evaluated the effect of daily oral administration of an herbal preparation containing high dosage of curcumin (HPC) on EBC in COPD patients.

**Materials and methods:** 10 COPD (8 M, age 63.3 ± 7.9) were evaluated at baseline (T0) and after 12 weeks (T1) of oral administration of HPC once a day collecting each visit EBC, clinical score (BSCN) and spirometry.

**Results:** We have detected various profiles of semi-volatile organic compounds (SVOC) in EBC in patients with COPD, asthma and healthy subjects. Mathematical approach to available data revealed 9 SVOC which have been deemed the most appropriate for solving recognition problem (2-phenoxethanol, decanol-1, ethyl 2,3-dihydro-1H-inden-1-ol and others). EBC profiles of healthy subjects can be distinguished from patients with asthma with reliability 75%, healthy subjects from COPD patients with reliability 85% and asthma patients from COPD patients with reliability 83%.

**Conclusion:** Metabolomic analysis of EBC can discriminate patients with asthma and COPD and healthy subjects. We propose that differences in SVOC profiles between asthma and COPD are disease related.

**P4794**

**Development of mass spectrometry approaches to quantifying lipid mediators in airway disease**

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**Background:** Lipid mediators (LMs, such as prostaglandins and leukotrienes) have been extensively studied for their role in both the onset and resolution of inflammation in airway diseases. We report here the development of a state-of-the-art approach for the detection and quantification of lipid mediators in airway disease. Using a data-driven, machine learning approach, we have developed an MS-based method for the rapid and sensitive detection of LMs in airway disease. This method is based on a combination of targeted and non-targeted approaches and is designed to detect a wide range of LMs. Additionally, we have developed a novel approach for the quantification of LMs in airway disease. This approach is based on the use of a multi-plexed MS assay and is designed to detect a wide range of LMs in a single sample. The results of this study demonstrate the potential of MS-based approaches for the rapid and sensitive detection and quantification of lipid mediators in airway disease. These results have important implications for the diagnosis and treatment of airway disease.
the-art quantitative lipodomics-based method for the analysis of LMs using Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS).

Aims: Develop a sensitive LC-MS/MS platform to quantify LMs from multiple biological matrices including urine, bronchoalveolar lavage fluid (BALF) and sputum. The method should encompass LMs from arachidonic (AA), linoleic (LA), dihomo-γ-linolenic (DGLA), α-linolenic (α-LA), eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acid pathways.

Methods: Pooled BALF from patients with sarcoidosis (n=5) was extracted by Solid Phase Extraction and analytes were quantified by LC-MS/MS (Acquity-Ultima, Waters). The method assessed 87 LMs in combination with 16 deuterated internal standards.

Results: In BALF from sarcoidosis patients, 29 LMs from six fatty acid were detected, but only 8 LMs from each of the AA and LA pathways were quantifiable. The fatty acid origin and biosynthesis pathway of the 29 LMs is shown in Fig. 1.

Conclusions: LC-MS/MS methods for LM quantification are applicable for exploring the etiology and pathology of respiratory diseases as exemplified with BALF from sarcoidosis patients. These methods will be useful in examining inflammatory processes.

P4795
Follow up of lung transplant recipients using electronic nose
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Background: The close follow up of lung transplant patients is essential in the recognition of both early and late complications, however today these can be confirmed only by invasive techniques. Analysis of exhaled breath might be promising, as various studies showed relationship between breath components and the development of BOS in lung transplant recipients. Electronic nose is able to analyse the peculiar pattern of breath (breathprint), and it discriminated different lung diseases successfully, however lung transplant patients were not studied yet.

Aim: To investigate the relationship between breathprint and various clinical parameters in lung transplant recipients.

Methods: Sixteen patients following lung transplantation participated in our study (mean age 39±14). The study had a model (N=25 samples) and a validation part (N=35 samples). Hence, in average 3.7±2.5 samples per patient were analysed. During their scheduled follow up at the outpatient clinic exhaled breath collection (N=35 samples). Hence, in average 3.7

Results: Median EWT post 16mins 33 13 mins 57

Conclusions: The analysis of exhaled breath can be useful in the follow-up of patients with obstructive pulmonary disease. The relation with the drug level draws attention to the interfering effect of treatment and to the possibility of monitoring drug level by exhaled breath testing.

P4796
Profiling of sputum inflammatory mediators in asthma and chronic obstructive pulmonary disease
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Introduction: Asthma and chronic obstructive pulmonary disease (COPD) display features of overlap in airway physiology and pulmonary inflammation. The relationship between mediator expression and airway inflammation was explored within these airway diseases.

Methods: Patients with asthma (54 patients: 21 men) and COPD (49 patients: 36 men) were studied. Clinical characteristics and sputum was collected at entry into the study. A two-step sputum processing method was performed for supernatant and cytopsin preparation. The Mesoscale Discovery and Lumixin platforms were used to measure cytokines, chemokines and matrix metalloproteinase levels.

Results: Analytes sensitive to dithiothreitol (DTT) that had increased recovery in the two step sputum process were IL-1β, 4, 5, 10, 13, IFN-γ, TNFRI, GM-CSF, CCL2, 3, 4, 5, 13 and 17. There was a differential expression in IL-8, TNFRI and TNFRII between asthma and COPD (mean fold difference (95% confidence interval) IL-8, 2.6 (1.3 to 5.4), p=0.01; TNFRI, 2.1 (1.3 to 5.4), p=0.03; and TNFRII, 2.6 (1.2 to 5.6), p=0.02). In neutrophilic and eosinophilic airway inflammation, TNFα, TNFRI, TNFRII, IL-6, IL-8 and IL-5 could differentiate between these phenotypes. However, these phenotypes were unrelated to the diagnosis of asthma or COPD.

Conclusion: Recovery of sputum mediators sensitive to DTT can be improved using a new sputum processing technique. Within airway inflammatory subphenotypes there is a differential pattern of mediator expression that is independent of disease. Whether these inflammatory phenotypes in asthma and COPD confer distinct pathogenesis, therapeutic responses and clinical phenotypes needs to be further evaluated.

494. Pulmonary rehabilitation: looking at alternative approaches and alternative populations beyond COPD

P4797
Pulmonary rehabilitation: First line treatment for respiratory disease
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Introduction: Breathing Space is a multi-disciplinary primary care centre for the management of respiratory conditions in Rotherham. England. Breathing Space has an emphasis on Pulmonary Rehabilitation (PR) incorporating outpatient pulmonary rehabilitation and an inpatient facility.

Aims: The aim of the research was to establish the effect of PR on Patient Recorded Outcome Measures.

Methods: Data was examined retrospectively between June 2007 and December 2010. All patients underwent field walking tests (Incremental Shuttle Walk Test (ISWT), Endurance Walking Test (EWT) or 6 Minute Walk Test (6MWT)) and CRQ (self report) and HAD questionnaires. PR was provided over 12 sessions in a 6 week period.

Results: 94 patients with Bronchiectasis or Pulmonary Fibrosis were referred for PR. Of these 95% (n=78) agreed to attend PR after assessment. Refer to tables 1 & 2 for results.

Results for walking tests

<table>
<thead>
<tr>
<th></th>
<th>Bronchiectasis</th>
<th>Pulmonary Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited</td>
<td>74% (n=60)</td>
<td>26% (n=22)</td>
</tr>
<tr>
<td>Female</td>
<td>57% (n=34)</td>
<td>41% (n=29)</td>
</tr>
<tr>
<td>Completion rate</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Mean ISWT pre</td>
<td>215M</td>
<td>207M</td>
</tr>
<tr>
<td>Mean ISWT post</td>
<td>288M*</td>
<td>136M*</td>
</tr>
<tr>
<td>Mean 6MWT pre</td>
<td>108M</td>
<td>70M</td>
</tr>
<tr>
<td>Mean 6MWT post</td>
<td>138M</td>
<td>95M</td>
</tr>
<tr>
<td>Mean EWT pre</td>
<td>6min 39</td>
<td>4min 52</td>
</tr>
<tr>
<td>Mean EWT post</td>
<td>6min 33</td>
<td>13 mins 57</td>
</tr>
</tbody>
</table>

*Denotes clinically significant result.

Results of Health Status Measures

<table>
<thead>
<tr>
<th></th>
<th>Bronchiectasis</th>
<th>Pulmonary Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CRQ-SR Pre</td>
<td>Dyspnoea</td>
<td>3.13</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>3.07</td>
</tr>
<tr>
<td></td>
<td>Emotion</td>
<td>4.10</td>
</tr>
<tr>
<td>Mean CRQ-SR Post</td>
<td>Mastery</td>
<td>4.11</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>3.76*</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>3.90*</td>
</tr>
<tr>
<td></td>
<td>Emotion</td>
<td>4.78*</td>
</tr>
<tr>
<td></td>
<td>Mastery</td>
<td>4.20</td>
</tr>
<tr>
<td>HAD anxiety pre</td>
<td>post</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>6.0*</td>
</tr>
<tr>
<td>HAD depression pre</td>
<td>post</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>6.05*</td>
</tr>
</tbody>
</table>

*Denotes clinically significant result.
Conclusion: Our data suggests that PR for patients diagnosed with Bronchiectasis or Pulmonary Fibrosis should be the treatment of choice.

P4798

Effect of pulmonary rehabilitation on gas exchange, muscle cross sectional area and functional parameters in interstitial lung disease

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Introduction: Pulmonary rehabilitation has an important role in the management of interstitial lung diseases (ILD). This study evaluates effect of pulmonary rehabilitation on gas exchange, muscle cross sectional area and functional parameters in patients of ILD.

Aims and objectives: To evaluate 6 minute walk distance (6MWD), Mid Thigh Cross Sectional Area on CT (MTCSACT) and Carbon Monoxide Diffusion Capacity (DLCO) before and after pulmonary rehabilitation in patients of ILD.

Methods: Twenty eight patients of ILD were randomly allocated to Control and Test groups. The control group received standard medications for 8 weeks while the test group was given supervised pulmonary rehabilitation along with standard medications for 8 weeks.

Results: Mean values of 6MWD changed from 476.50±61.97 m to 482.64±58.33 m in control group [p=0.369] and from 455.46±63.55 m to 509.78±69.03 m in test group [p=0.015]. Levels of DLCO changed from 11.88±3.87 ml/min/mmHg to 11.92±3.73 ml/min/mmHg in control group [p=0.390] and from 89.81±5.73 ml/min/mmHg to 13.08±6.37 ml/min/mmHg [p=0.004] in test group. Mean values of MTCSACT changed from 9311.21±1918.42 cm² to 9485.21±2083.44 cm² in control group [p=0.066] and from 9485.21±2083.44 cm² to 10303.7±2137.41 cm² in test group [p=0.031].

The difference of means between control and test group after pulmonary rehabilitation was significant for DLCO, MTCSACT, and 6MWD. Positive correlation was obtained between MTCSACT and 6MWD with 0.7, p=0.006.

Conclusion: Pulmonary rehabilitation causes significant improvement in muscle cross sectional area and functional parameters in ILD patients along with significant improvement in gas exchange.

P4799

Pulmonary rehabilitation (PR) outcomes in chronic obstructive pulmonary disease (COPD) compared with interstitial lung disease (ILD)

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Background: PR is effective in improving exercise capacity, dyspnea and quality of life in patients with COPD. The benefits in patients with ILD are less well described.

Methods: The records of 24 patients (15 male) with ILD who had completed PR were compared with age (within 2 years) and MRC score (same score) matched COPD patients (19 male) who had also completed PR within the same setting. Incremental shuttle walk distance (ISWT), endurance shuttle walk time (ESWT), level of exercise induced desaturation, chronic respiratory disease questionnaire (CRQD) scores and hospital anxiety and depression (HAD) scores were measured at baseline and on completion of the 8 week programme. The mean changes in each group were compared using a paired t-test.

Results: The mean average age of each group was 68 years, with a mean average MRC score of 3.3. The baseline oxygen saturations in both groups was similar.

Differences in outcomes between COPD and ILD groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>COPD</th>
<th>ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔISWT (m)</td>
<td>36.2</td>
<td>31.5</td>
</tr>
<tr>
<td>ΔESWT (seconds)</td>
<td>506.1</td>
<td>303.7</td>
</tr>
<tr>
<td>ΔDyspnea (CRQD)</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>ΔMastery (CRQD)</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>ΔEmotional function (CRQD)</td>
<td>4.1</td>
<td>3.7</td>
</tr>
<tr>
<td>ΔFatigue (CRQD)</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>ΔAnxiety (HAD)</td>
<td>-1.1</td>
<td>-1.4</td>
</tr>
<tr>
<td>ΔDepression (HAD)</td>
<td>-1.8</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

Both groups showed improvements in all measured outcomes-most of which were clinically important. There was no statistically significant difference between the groups in any of the outcomes. In addition, the level of exercise desaturation after PR was greater in the ILD group (7.7%) compared with the COPD group (3.0%).

Conclusions: This study shows that PR in patients with ILD produces similar outcomes to those seen in COPD. The exercise induced oxygen desaturation seen in patients with ILD is greater. Outcomes to those seen in COPD. This study shows that PR in patients with ILD produces similar outcomes to those seen in COPD. The exercise induced oxygen desaturation seen in patients with ILD is greater.

P4800

Exercise tolerance and symptoms after standard rehabilitation in emphysema-like COPD patients

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In this retrospective analysis on a cohort of 823 COPD patients (age 71±8 yrs, FEV1 56±18% pr.) admitted in 3 centres, we aimed at describing the effect of standard rehabilitation on exercise tolerance and symptoms in the subgroup of emphysema-like individuals, as defined by lung function parameters.

Pre-to-post changes (D) in exercise tolerance (6MWT), Borg dyspnea (D), fatigue (F) and SaO2 nadir (N) on effort, perceived breathlessness (MRC), and quality-of-life (SGRQ) were reported. Propotion of patients reaching the minimally clinical important difference (MCID) in 6MWT, D, F, MRC and SGRQ were also recorded.

Outcomes were then compared between the Emphysema (E, n=283) and the COPD (C, n=540) subgroups.

Lung functions were different by definition when comparing the two groups, with similar age, body mass, exercise tolerance, and breathlessness at baseline. D-6MWD (+72±47 and +62±42 m, p=0.002), D-F (-2±3.1 and -1.9±1.6 points, p=0.002), D-F (+2.8±1.9 and -1.9±1.6 points, p=0.070), and D-N (+1±4.3 and +0.5±1.3 point, p=0.002) were higher, whereas a larger proportion of patients improved at the MCID in 6MWT (62% and 54%, p=0.040) in group E when compared with group C. Using a multivariate logistic regression model, we found that higher normalised PaO2, and lower 6MWT, and FRC at baseline significantly correlated with D-6MWT in the E group (p<0.01).

This study generates the hypothesis that COPD patients with emphysema phenotype are more likely to gain exercise tolerance and perceived symptoms after standard rehabilitation.

P4801

Does better endurance capacity increase physical performance and work participation for patients with obstructive pulmonary disease?

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Background: Patients with chronic lung disease have increased risk of unemployment and disability pensioning caused by exacerbations and the complexity of this disease. Multidisciplinary pulmonary rehabilitation could be expected to improve physical performance, work stability and social participation.

Aim: The aim of this study was to evaluate if a 4 weeks’ multidisciplinary vocational pulmonary rehabilitation had an effect on endurance capacity, and whether a change was correlated with degree of physical activity and work participation 1, 6 and 12 months post-rehabilitation.

Methods: 128 consecutive patients were included in this intervention prospective cohort study. Endurance capacity was measured as time to exhaustion during constant work load treadmill walk before and after rehabilitation. Data on post-rehabilitation work relations and physical performance was collected by telephone interview.

Results: The endurance capacity increased from 360 sec to 840 sec (median), p=0.000 during the 4 weeks of rehabilitation. Increase in treadmill endurance time was correlated with physical activity 6 months (r=0.22, p=0.023), but not 12 months post-rehabilitation (r=0.03, p=0.776). There was no correlation between increase in treadmill endurance and work participation 6 or 12 months after rehabilitation.

Conclusion: Patients experiencing the largest improvement in physical endurance after participation in the current rehabilitation model were most likely to continue their physical activity 6 months after rehabilitation, but the effect was lost after 12 months. The degree of improvement in physical condition did not influence work participation.

P4802

Exercise physiologic response during three different video games in cystic fibrosis patients

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Cystic fibrosis (CF) is a multisystemic disease characterized by an abnormal ventilation response that limits the exercise tolerance. Physical training increases exercise capacity, decreases dyspnea and improves quality of life. Adherence to respiratory rehabilitation programs is a key factor to guarantee optimal benefits. To determine the efficiency of three Wii video games as training systems by analysing the physiologic response in CF.

Methods: We included 24 CF patients: age 12±3.7 years; BMI: 18.3±8; FVC: 97±20%; FEV1: 93±20%, followed 4 different exercise types in randomized order
**WEDNESDAY, SEPTEMBER 28TH 2011**

**P4803**

Physical rehabilitation in asthma management

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1Department of Clinical Immunology and Allergology, Saratov State Medical University, Saratov, Russian Federation; 2IMI, IMI University Centre, Luzern, Switzerland

**Background:** 50% of asthma patients experience limitations in physical activity and usual lifestyle. Gymnastics can provide significant health benefits and improve quality of life.

**Objective:** To investigate effects of gymnastics on asthma patients, specifically leading to ameliorated lung function.

**Methods:** A prospective, randomized, controlled trial was performed to evaluate the effect of respiratory gymnastics (RG). 85 patients with moderate/severe asthma were randomly assigned to control (CG - 16 persons, standard therapy) or RG (RGTG - 69 persons, standard therapy & RG group) with no significant difference in demographics. Patients were instructed how to practice exercises and examined in 3-6-9-12 months for pulmonary function, cardiopulmonary exercise and control of asthma.

**Results:** 12 month physical rehabilitation (with pharmacotherapy) reduced: the frequency of complaints, clinical manifestations of asthma; symptoms: daytime (from 8.5±3.2 to 4.5±2.7; p < 0.0001) and night (from 54.7±7.1 to 44.6±6.9; p = 0.0001); the consumption of β2-agonists (from 3.2 to 2.1 puffs/week). RGTG group increased: FEV1 (from 1.3 to 1.7 L); PEF (from 338±6.19 to 403±5.18); exercise capacity (W/kg) from 0.85±0.1 to 1.4±0.2. The number of patients with limited physical activity decreased from 86.0±5.0 to 22.0±5.9; p = 0.001. Heart rate and blood pressure recovery time after exercise decreased from 10.4±0.7 to 9.1±0.6 min (p < 0.05). CG changes were much lower (difference between groups was significant, p < 0.001).

**Conclusions:** Individual programs of RG reduced asthma symptoms and the use of bronchodilator medication in patients with asthma, and can be effective as an adjuvant therapy and optimize asthma patients medical treatment.

**P4804**

Obesity in COPD and the response to pulmonary rehabilitation

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The obesity paradox is well recognized in COPD. Obese (OB) patients with COPD may have better survival than the non-OB, yet obesity may impair lung function, increase respiratory load and dyspnea. We hypothesized that OB COPD patients referred to pulmonary rehabilitation (PR) would have reduced exercise capacity and quality of life compared with normal weight (NW) COPD patients, and would respond less well to PR. As BMI<21 is associated with worse prognosis, we defined NW as a BMI of 21-24.9. OB was defined as BMI 30 plus. In 218 patients referred to an 8-week outpatient PR program, we identified 64 NW and 67 OB patients. Baseline and post-PR incremental shuttle walk (ISW), self-report Chronic Respiratory Disease Questionnaire (CQDQ), MRC Dyspnea score (MRC-D), Hospital Anxiety and Depression (HAD) scores and fat free mass (FFM) were recorded. Despite less severe airflow obstruction in OB patients (Median IQR FEV1% predicted: NW = 40 (26, 62) vs. OB = 62 (42, 76); p < 0.0001), median ISW (m) was reduced (NW = 185 (120, 295) vs. OB = 105 (50, 255); p<0.01). CRQD-SR was also significantly reduced (p=0.02) in OB patients. Following PR, there was a significant improvement in ISW, CRQD-SR, MRC and HAD-D in OB patients. No significant difference was seen in pre- to post-PR changes in ISW, CRQD-SR, MRC, HAD and FFM between the 2 groups. Obesity in COPD was associated with less impairment in respiratory function, but worse exercise capacity and quality of life. However OB patients responded equally well to PR as NW patients. The impairment of exercise capacity and quality of life in OB COPD patients may lead to presentation to health care professionals at an earlier stage of lung function impairment and may explain the obesity paradox.

**P4805**

Outpatient vs. home-based pulmonary rehabilitation in COPD: A randomized controlled trial

Julio Cesar Oliveira1, Fernando Sergio Leitão Filho3, Luciana Sampaio3, Ana Carolina Oliveira1, Raquel Hirata2, Dircce Costa2, Claudio Donner4, Luis Vicente Oliveira1, 1Pulmonary Rehabilitation, Lung Institute, Cacacel, PR Brazil; 2Rehabilitation Sciences Master’s Program, Nove de Julho University, Sao Paulo, SP Brazil; 3Medicine Department, Fortaleza University, Fortaleza, CE, Brazil; 4Ambulatorio Diagnostico e Terapeutico Polispecialistico, MONdo Medico, Rorosmanuro, Italy

**Introduction:** Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and mortality affecting a large number of individuals in both developed and developing countries and it represents a significant financial burden for patients, families and society. Pulmonary rehabilitation (PR) is a multidisciplinary program that results in an improvement in dyspnea, fatigue and quality of life. Despite its proven effectiveness and the strong scientific recommendations for its routine use in the care of COPD, PR is generally underutilized and strategies for increasing access to PR are needed. Homebased self-monitored pulmonary rehabilitation is an alternative to outpatient rehabilitation. In the present study, patients with mild, moderate and severe COPD submitted to either an outpatient or home PR program for 12 weeks were analyzed.

**Methods:** Patients who fulfilled the inclusion criteria were randomized into three distinct groups: an outpatient group who performed all activities at the clinic, a home-based group who performed the activities at home and a control group. PR consisted of a combination of aerobic exercises and strengthening of upper and lower limbs 3 times a week for 12 weeks.

**Results:** There was a significant difference in the distance covered on the six minute walk test (p<0.05) and BODE index (p<0.001) in the outpatient and home-based groups after participating in the rehabilitation program compared to baseline.

**Conclusion:** A home-based self-monitoring pulmonary rehabilitation program is as effective as outpatient pulmonary rehabilitation and is a valid alternative for the management of patients with COPD.

**P4806**

Improvement in skeletal muscle dysfunction after twice-weekly exercise training in COPD patients

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1Health Sciences Department, Public University of Navarre, Tudela, Navarre, Spain; 2Respiratory Division, Complejo Hospitalario de Navarra, Pamplona, Navarre, Spain; 3Studies, Research and Sport Medicine Center, Institute of Sport, Government of Navarra, Pamplona, Navarre, Spain

**Introduction:** Skeletal muscle dysfunction is one of the extrapulmonary effects in patients with COPD, resulting in reduced peripheral muscle strength and functional capacity and have been associated to increased mortality risk. It is unknown the optimal frequency of exercise training to optimize the effectiveness of rehabilitation.

**Aim:** To compare the effects of the 12-wk training period of low-volume frequency on maximal strength and muscle power.

**Methods:** Thirty-six moderate to severe COPD men were divided into resistance group (RG, n=14), combined group (REG, n=14) and control (COG, n=8). RG performed a low volume exercise training for 12 weeks. The subjects were tested for maximal strength in the leg press (1RMp), lower limb power at 70%IRM (P70IRMp), maximal strength in chest press (1RMcp) and seated row (1RMgr). Statistical analyses were performed with SPSS.

**Results:** 1RMp increased 28% (from 191±52 to 238±68kg, p<0.001) in REG, 33% (from 189±56 to 250±89kg, p<0.001) in RG and was higher (P<0.05) than in the CG. 1RMcp increased 31% (from 50±12 to 66±18kg, p<0.001) in RG, 35% (from 51±17 to 67±17kg, p<0.001) in REG and was higher (P<0.001) than in the CG. 1RMgr increased (P<0.001) 31% in REG and 41% in RG compared to CG. P70IRMp increased 50% (from 557±290 to 725±258 w, p<0.001) in REG, 33% (from 601±167 to 797±212 w, P<0.001) in RG.

**Conclusions:** Twice-weekly resistance exercise improves lower and upper body maximal strength and lower muscle power in COPD. Once-weekly resistance training is as effective in eliciting improvements in maximal strength and muscle power as twice-weekly resistance training.

Supported by Ministry of Education of Spain and Health Department of Navarre

**P4807**

Interest of neuromuscular electro-stimulation (NMES) in COPD patients during an ambulatory comprehensive respiratory rehabilitation program

Delphine Nguyen Dang1, Michael Gluck2, Freddy Pimay3, Renaud Lous1, Marc Vanderhornen1, 1Respiratory Diseases, CHU, Liege, Belgium; 2Department of Physic Medicine and Rehabilitation, CHU, Liege, Belgium

**Introduction:** COPD often leads to peripheral muscle atrophy and weakness.
Peripheral muscle electrostimulation: Cardiovascular response in COPD patients and long term effects
Bruno-Henri Marchand, Marine Houle-Pilouquin, Pierre Claude. Respiratory Medicine, Centre Hospitalier Universitaire de Montréal, Montréal, QC, Canada.

Conventional pulmonary rehabilitation (PR) suppose minimal active exercise. Because of the ventilatory limitation, severe COPD patients are not always able to fully participate. Electrostimulation (ESM) of the peripheral muscles helps to prevent total unuse of the patients muscles and could aim to a complete PR program. The long-term benefits of this intervention may be evanescent. The cardiovascular effects of ESM are not known in severe to very severe COPD patients.

We prospectively studied 9 COPD patients (3 females and 6 males, mean age of 65 y/o, mean FEV1 of 0.78 L, 28%) undertaking home-based peripheral muscles ESM. This latter consisted of 5 periods of 20 minutes, 5 times a week and for 3 weeks. Short and long term benefits were measured according to 6MWT and 1RM leg press test. Cardiac frequency (F) and arterial pressure (AP) were registered each 5 minutes during periods 1, 7 and 15. F and AP did not show any significant fluctuations from beginning to end of the ESM period, and there is no difference between periods 1 and 15. 6MWT showed a median change of 14% (p=0.001), and significant improvement of Heart Rate reserve (HRR) of 244 m/s (p=0.002). The 1RM leg press was also improved (192 to 209 p, p=0.004). After, 3/9 patients were able to complete a PR program. At one year, 6MWT and 1RM leg press test were above the baseline values. ESM was well tolerated by the patients, without complication.

Conclusion: Home-based ESM program is a safe procedure and is not associated with significant change in F and AP, and an immediate impact was observed on 6MWT and 1RM leg press test. It could precede a complete PR program in selected severe to very severe COPD patients and be offered in a context of hospitalization.

The effect of BiPAP on maximum exercise capacity in patients with COPD
Ana-Maria Mogu1, Michel De Marche2, Stéphane Delisle2. Jadrinka Spahija1,2. 1School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada; 2Respiratory Health Research Center, Sacré-Cœur Hospital, Montreal, QC, Canada.

Methods: A randomized controlled design was used. Ten stable COPD patients (FEV1; 33±21% pred) performed three symptom-limited incremental exercise tests on a bicycle ergometer while breathing through a mouthpiece, with either no pressure support (PSno), PS of 0 cm H2O (PS0, IPAP & EPAP 4 cm H2O) or 10 cm H2O (PS10, IPAP 14 & EPAP 4 cm H2O) of assist on separate days. Exercise test ended at ventilatory (VL), dyspnea and leg effort (Borg), end-expiratory lung volume (EELV), breathing pattern, O2 uptake (VO2) and CO2 production (VCO2) were measured during exercise.

Results: Peak WL was lower with PS10 (33±16) and PS0 (30.5±13) than PSno (43±19) (p<0.001), there was no difference between PS0 and PS0. Dyspnea at peak exercise was similar with PSno, PS0 and PS10; at isoclair it was lower or PSno compared to PS10 and PS0 (p<0.01). Leg effort at peak exercise was higher with PS10 than PS0 and PS0 (p<0.05), whereas it was not different at isoclair. Tidal volume (VT) and minute ventilation (VE) were highest with PS10 and lowest with PSno both at peak exercise (p<0.001) and isoload (p<0.001). EELV was similar at peak exercise with all three conditions. VO2 and VCO2 were greater with PS10 and PS0 than PSno (both p<0.001), both at peak exercise and isoload.

Conclusion: Use of BiPAP during incremental exercise in the absence of a plateau exhalation valve increases VT and VE at the expense of increasing the VO2 and dyspnea, which in turns reduces peak exercise WL in COPD patients.

Effect of ADL-training for persons with COPD: A randomized controlled trial
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Background: Due to various degrees of breathlessness, fatigue, coughing and increased spasm production, COPD patients have problems performing activities of daily living (ADL). Aim: To investigate if COPD patients experienced differences in performance and satisfaction in performing ADLs at 1 hour compared to 1 hour ADL-training during a 4 weeks pulmonary rehabilitation program.

Methods: A prospective, randomized, single blinded, parallel group design. The control group received Glittrleklinikken’s standard rehabilitation program, which included 1-60 min ADL-training. The experimental group received 4-60 min ADL-training in addition to the standard rehabilitation program. The Canadian Occupational Performance Measure assessed the performance and satisfaction of doing ADL at inclusion (baseline), after four weeks (at discharge) and three months after discharge.

Results: 24 COPD patients (59% women) were included; mean±SD age 69±8 years. FEV1% predicted 35% ± 19). FEV1% predicted change 43±14%, as well as significant change in F and AP, and an immediate impact was observed on maximum exercise capacity (p<0.001), both at peak exercise and isoload.

Conclusion: The patients with COPD participating in a 5 hours ADL-training program evaluated their performance and satisfaction of doing ADL to be better than those participating in a 1 hour program, both at the time of discharge and three months after discharge.

Comparison of efficacy of respiratory rehabilitation in patients with COPD and interstitial lung disease
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Objectives: There are few reports describing the efficacy of pulmonary rehabilita- tion (PR) in patients with interstitial lung disease (ILD). We studied whether PR could improve functional status and dyspnea in a group of patients with ILD in comparison with patients with COPD.

Methods: Seventy three outpatients (mean age 71y, male: female = 57:16, ILD: COPD: others = 22: 36: 15) joined a 12-week PR program including exercise training, physiotherapy and education. Six-minute walking test, lung function test COPD: others = 22: 36: 15) joined a 12-week PR program including exercise training, physiotherapy and education. Six-minute walking test, lung function test and quality of life were measured at baseline and 12 weeks after discharge.

Results: We found substantial decrease in SGRQ score from 42.1 to 33.9 (p <0.0409) in total patients. Patients with ILD responded well to the program with the improvement of 6-minute walking distance (318.4 m to 331.6 m) and Borg score (5.2 to 4.4). There was no difference between the level of improvement in patients with COPD and ILD.

Conclusion: Our results show that PR improves both functional status and dyspnea in patients with ILD to the same extent as with COPD. PR should be considered as a standard of care for ILD patients.

Pulmonary rehabilitation in patients with interstitial lung disease – An useful therapeutic option?
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Introduction: Pulmonary rehabilitation (PR) is recommended for patients with chronic lung diseases by ATS or ERS independent of underlying disease. Data examining the role of PR in patients with interstitial lung disease (ILD) are limited.
so far only a benefit of PR in patients with COPD is widely accepted. Aim of our study is to evaluate an in-patient training in view of functional status and quality of life in COPD-patients. Therefore PR should be considered as a standard of care for patients with ILD.

P4813
Stationary bicycle training at home in COPD patient on LTOT. Is it enough to improve quality of life and exercise capacity? A pilot study
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Pulmonary rehabilitation improves quality of life (QoL) and exercise capacity (EC) in COPD patients. LTOT with stationary source may reduce daily activities (DA). Aim of study was to assess if self administered training at home improves QoL, EC and reduces symptoms restriction in DA.

Methods: Consecutive COPD pts qualified for LTOT with oxygen concentrator were assessed and randomly assigned to training (TG) or control (CG) groups. Assessment comprised of: cardiopulmonary exercise test (CPET) on cycle ergometer, 6 minute walk test (6MWT), dyspnoea (MRC scale), lung function tests, QoL (SGRQ), DA measured by actigraphy and questionnaire. Training consisted of 30 min. cycling every day for 3 months. In TG adherence to training and its intensity were monitored by memory card. Pts were regularly visited and load was adjusted to patients ability. CG was monitored by phone and encouraged to sustain physical activity.

Results: We studied 33 pts (18M, 15F), mean age 70±9 yrs, mean FEV1 0.9±0.4 (40±13%), mean PaO2 45±4 mmHg. Of 20 pts allocated to TG, 13 pts completed training program. Adherence was satisfactory, pts trained 73±23% of days. TG showed significant improvement in SGRQ (symptoms) and duration of CPET. There was tendency to improve VO2max (p=0.054) and total SGRQ score (p=0.07). Better adherence to training correlated with greater improvement in QoL, VO2max and 6MWT distance. Higher workload reached during training correlated with reduction of symptoms and improvement in 6MWT, dyspnoea (MRC scale). Further analysis is ongoing.

Conclusions: Self cycling at home may improve QoL and EC in COPD patients starting LTOT with stationary source, but has no effect on performance of DA.

P4814
Pilot study of effectiveness of home rehabilitation for homebound patients with severe COPD
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Introduction: While pulmonary rehabilitation is efficacious, available evidence is not generalizable to patients who are homebound with severe impairment.

Objective: To test the effectiveness of home-based rehabilitation for homebound patients with physician-diagnosed COPD and severe functional impairment.

Methods: Homebound patients, defined as not driving independently and requiring taxing effort to leave home, were enrolled from primary care and pulmonary clinics. Patients were randomly assigned to one of two interventions comprised of education and physical therapy emphasizing either active (A) or strengthening (S). The interventions were delivered over 8 weeks with up to 20 sessions. Pre- and post-intervention outcome measures were collected at 8 and 16 weeks using the Chronic Respiratory Questionnaire (CRQ) and 2-minute walk distance (2MWD).

Results: Of 41 patients enrolled 24 completed the 8 week intervention period with mean age 74.4 (SD 10.7) years, 45.8% female, FEV1 0.75L (30% predicted). Baseline 2MWDs (time, SD) were 56.0m (23.3) and 16.9m (34.0) for groups A and S respectively. After 16 weeks all CRQ domains improved in both groups with the largest improvements in CRQ-dyspnea (A=1.85 [p=0.02] and S=2.21 [p=0.003]). Overall, the proportion of patients reporting clinically significant improvement on CRQ-dyspnea was 80% in group A and 71% in group S. Moreover, 2MWD increased in Group A but declined in Group S.

Conclusions: These results suggest that among homebound patients with severe COPD 8-weeks of either aerobic or strength training are effective for improving quality of life, but aerobic training may be needed to improve walking distance.

P4815
Transparency in evidence-based pediatric asthma guidelines: GRADE and the other considerations
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Introduction: International evidence-based pediatric asthma guidelines are often not used in clinical practice. In step 3 of pediatric asthma management some guidelines make clear choices for LABA were others give alternative options, but without being transparent in why choices are made. To enhance the usefulness of guidelines, the ATS has chosen GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) as the preferred methodology for rating the quality of evidence and strength of recommendations in clinical practice guidelines.

Objective: Our aim was to develop transparent recommendations on step 3 of asthma management in children.

Methods: We used GRADE to assess the quality of evidence and separately reported other considerations. Final recommendations were formulated on both evidence as well as the other considerations in cooperation with the Dutch Society of Pediatric Pulmonologists.

Results: We found 7 RCTs comparing doubling the dose of ICS versus a combination of ICS and LABA and/or versus LTRA in children with symptomatic asthma despite normal ICS dose. According to GRADE, the quality of evidence was "moderate", both treatments were effective and individual response could not be predicted. Other considerations included safety, convenience and costs. We suggest in children with symptomatic asthma despite ICS, to first double the dose of ICS. If not effective, a combination of ICS and LABA can be prescribed. In case of adverse effects or poor inhalation technique a LTRA can be prescribed.

Conclusion: By using the GRADE approach together with other considerations clear recommendations for step 3 in asthma management were made. This approach might improve implementation.
Aim: To investigate the association between current and long-term asthma control. Methods: Children aged 2-6 yrs, who received a prescription for (ICS) by their general practitioner in the past year and who were still using ICS at the time of inclusion, were followed up for 3 months, during which adherence to ICS therapy was compared to investigate agreement. Results: 106 children (mean age 4.3 yrs) had an ICS prescription over the past year. 95 children could be reached by telephone, 82 of whom were willing to provide information about current ICS use and symptoms of their child. 30 patients (36%) used ICS intermittently during symptomatic episodes, 24 (29%) patients used ICS for non-specific respiratory symptoms such as cough or for intermittent symptoms such as an isolated wheeze episode. 28 children (35%) were using ICS regularly, 21 of whom consented to electronic adherence measurement for 3 months. In these 21 patients, median adherence was 81% [range 34-97%] of prescribed dosages. Conclusion: The low adherence to ICS in population studies of children with asthma may be partly explained by inappropriate prescription of ICS to children with intermittent episodes of wheeze, and non-specific respiratory symptoms such as cough. High adherence to ICS treatment was found in those patients who received ICS therapy in accordance with international asthma guidelines.

P4819
Lack of behavioural problems in preschool children using inhaled corticosteroids with high adherence
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Background: Parents of young children are frequently worried about the potential side effects of asthma treatment on their child’s behaviour. Aim: To examine whether preschool children using inhaled corticosteroids (ICS) for asthma are more likely to have more behavioural problems compared with healthy reference group. Methods: We included 81 children 2-5 years of age with persistent asthma symptoms who were using ICS. During 3 months follow-up, adherence to ICS treatment was recorded by an electronic logging device (Smartinhales®). The parents completed the Child Behaviour Checklist (CBCL) to assess behavioural problems; results were compared to published reference groups of healthy children. Results: The median (interquartile range) adherence to ICS was 92 (78-97)%. There were no significant differences in CBCL scores (total, internalizing, externalizing problems) between children on ICS and healthy children (all p values > 0.2). Children with asthma were significantly more likely to have somatic complaints (p=0.001) and significantly less likely to have anxious/depressive symptoms (p=0.1) than the reference group. Conclusions: Maintenance treatment with ICS, taken daily as prescribed, is not associated with an increased risk of behavioural problems in preschool children.
Lemonia Tsartsali1, Marios Papadopoulos 1, Evagelia Lagona2, Salivary cortisol for assessment of hypothalamic-pituitary-adrenal (HPA) axis function evaluation. Diurnal SC variation may offer a dynamic response of serum cortisol to ACTH and may provide an alternative to the blood test for HPA axis function evaluation. A significant positive correlation was found between salivary and serum cortisol, beginning with SC at 0' (R:0.398, p=0.003; R:0.401, p=0.002) and SC at 60' (R:0.389, p=0.003; R:0.401, p=0.002; R:0.385, p=0.003; R:0.404, p=0.003) and SC at 0' (R:0.308, p=0.025; R:0.316 p=0.022; R:0.318, p=0.026) and SC at 0' (R:0.389, p=0.003; R:0.401, p=0.002; R:0.336, p=0.001; 30' R:0.402, p=0.002, 60' R:0.303, p=0.041; R:0.368, p=0.009).

Conclusion: The salivary low dose ACTH test yields results that parallel the response of serum cortisol to ACTH and may provide an alternative to the blood test for HPA axis function evaluation. Diurnal SC variation may offer a dynamic evaluation over a day with none intervention.

P4825 The oral corticosteroid sparing effect of omalizumab in patients with severe chronic asthma: Is there a difference when you become 12 years old? Samantha Moss, Michael Mceean, David Spencer. Respiratory Paediatrics, Great North Childrens Hospital, Newcastle upon Tyne, United Kingdom Omalizumab is licensed for treatment of severe persistent allergic asthma over the age of 6 years. In England and Wales, the National Institute of Clinical Excellence recommends omalizumab as a possible treatment for young people over the age of 12, but not before age 6 – 12.

We describe a population of children with severe asthma who have undergone a 16 week open label therapeutic trial of omalizumab.

The dose of oral corticosteroids at the start & end of the trial was documented. Some children completed modified quality of life and asthma symptom control questionnaires before and after the trial.

To date 15 children (13 boys) age 3-11 years, and 19 children (12 boys) age 11-16 years have completed a therapeutic trial in our centre. The baseline IGE was comparable between groups. We were able to reduce the daily corticosteroid dose in 13 children < 12 years (median pre 20, post 10 mg p=0.01) and in 16 children >12 years (median pre 10, post 5 mg, p=0.01). There was a significant increase pre- to post- trial in documented quality of life, using AQLQ (<12 n=8, >12 n=16), and asthma control (<12 n=8, >12 n=15) in all but 1 patient in each group.

In conclusion, the use of omalizumab in children with severe asthma may result in a clinically significant decrease in the use of oral corticosteroids and an improvement in quality of life and a reduction in asthma symptoms. In our practice omalizumab was as effective in children <12 years of age as in the older age group. A placebo controlled randomised control trial of omalizumab using steroid sparing as primary outcome in a paediatric population is urgently required.

P4826 Safety and efficacy of omalizumab in children with allergic asthma Judy Pitts1, Shahad Sheikh2, Karen McCoy3. 1Division of Pulmonary Medicine/Department of Pediatrics, Nationwide Children’s Hospital, Columbus, OH, United States; 2Division of Pulmonary Medicine/Department of Pediatrics, Ohio State University College of Medicine/Nationwide Children’s Hospital, Columbus, OH, United States

Background: Omalizumab (Xolair) is a humanized monoclonal antibody used in the treatment of adults and children over 12 years with moderate to severe allergic asthma. Pediatric studies are few.

Objectives: A retrospective chart review of pediatric patients who received omalizumab in the past 10 years for asthma at Nationwide Children’s Hospital, Columbus, Ohio.

Results: We had 13 patients, M:F 7:6, median age 13 years (range 9-17), median duration of therapy 36 months (range 1 to 59 months). 4 African American and 9 Caucasian, duration of asthma 15 years (9 to 16). Eight are still on therapy. All patients had severe persistent asthma. Twelve patients were receiving combination therapy (ICS and LABA). Only 4 patients claimed compliance with their asthma controller therapy. Five had family history of asthma, 6 had smoking exposure. Mean IGE before starting omalizumab was 249 (range 78 to 2664). Mean BMI was 25.7 and 46% of the patients were above the 100 percentile for BMI. Comparing between one year before and during omalizumab, mean hospital admission/patient/year decreased from 1.7±2.4 to 0.5±1.4 (p<0.05). There was also a trend towards improvement in ED visits from 2.3±3.2 to 1.7±3. Mean FEV1 during one year before omalizumab therapy, at initiation of therapy and during therapy was 91±18, 94±17, and 93±11 and was not statistically different. Two of 13 patients were taken off omalizumab because of serious side effects, one with anaphylaxis and second with dialated cardiomyopathy. Anaphylaxis was noted on first dose and cardiomyopathy was diagnosed in 5th year on therapy.

Conclusion: Omalizumab is add-on therapy in some patients with allergic asthma. Adverse reactions in children are limiting factor.
Methods: A single-blind, placebo-controlled trial was conducted in 60 mild persistent asthma children (5-14 y). Patients were randomly assigned to receive 5mg MT or placebo for 12 weeks. 30 healthy children (5-14 y) were as control. Clinical and laboratory parameters were determined throughout the trial. The mRNA expression of TGF-β1 in PBMC cells, subtypes of FoxP3+CD25− T cells and TGF-β1 in plasma were measured.

Results: After treatment, symptoms were improved with significant increase in pulmonary function in asthmatic, MT superior to placebo (p < 0.05). The mRNA expression of TGF-β1 and TGF-β1 level in asthmatic were lower than in control (0.31±0.07 vs. 0.67±0.2, p < 0.05 and 0.45±0.13 vs. 0.32±0.04, p < 0.05, respectively). Total FoxP3+, CD25− cell and CD25RA FoxP3− were higher in asthmatic (3.8%±1.3% vs 6.05%±1.8%, p < 0.007 and 4.66%±1.00% vs 3.27%±1.03%, p = 0.011, respectively). CD25RA FoxP3− was lower (0.75%±0.13% vs 0.93%±0.26%, p = 0.021). After treatment, CD25RA FoxP3− was increased in MT compared to placebo group (1.16%±0.24% vs 0.89%±0.22%, p < 0.01). TGF-β1 levels had no correlation with those levels of pulmonary function.

Conclusion: The expression of TGF-β1 was low in asthmatic children. Insufficient secretion of TGF-β1 and the deficiency in activating FoxP3+CD25− T cells might play an important role in pathogenesis of asthma. Up-regulation of expression of TGF-β1 and induction of expression of CD25RA FoxP3− in FoxP3+CD25− T cells by MT may be one of the mechanisms by which airway inflammation is inhibited in asthma.

P4829 Did inappropriate delivery systems hamper therapeutic efficacy of di-sodium-cromo-glycate (DSCG)? Time for a reappraisal
Manfred Keller, Oliver Denk, Albert Bucholski, Martin Knoch. Aerosol Research Institute, PARi Pharma GmbH, Graefelfing, Germany

Chymase-positive mast cells located in distal airways play a crucial role in asthma. Up-regulation of expression of TGF-β1 and the defection in activating FoxP3+CD25− T cells might play an important role in pathogenesis of asthma. Up-regulation of expression of TGF-β1 and induction of expression of CD25RA FoxP3− in FoxP3+CD25− T cells by MT may be one of the mechanisms by which airway inflammation is inhibited in asthma.

P4830 Designing a holding chamber mask using anthropometric data and CAD-simulation
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Background: A good seal is regarded as critical factor of face-masks for efficient inhalation drug delivery. Dead space, contour, flexibility and acceptance are also important.

Objectives: Evaluate anthropometric data and CAD-simulation to optimise face-masks for inhalation.

Methods: Basic anthropometric data of faces and heads from 32 children (age 1.1-3.5 yrs) were determined with measuring tape and calliper. Data were compared to existing literature data. Frontal and profile photos were taken with and without a mask prototype. Photographmetry was used to generate a 3-D CAD-database comprising the anthropometric and mask related information. The complex interactions between face and mask were then simulated and geometric data for optimised mask design determined. In a subsample (n=8) of the study population, fit of the optimised masks was visually controlled.

Results: Basic anthropometric data of the sample population agreed well with literature values, providing the study population to be representative. CAD-simulation identified the 2D-tightness geometry as inappropriate and was changed to a 3D-shape with soft lip seals. Dead space could be minimised yet leaving enough space for the nose to keep the mask comfortable. Design according to CAD-simulation led to an optimised fit of the face mask. Dimensions went very well with the children’s face structures. Enclosure of mouth and nose were both collision-free and space-saving.

Conclusions: Complex interactions between face and mask could be successfully simulated with a CAD-database. This helped to design face masks (PARi SmartTouch) which now allow for less leakage, more comfortable fit and minimised dead space - supporting efficient aerosol delivery.

P4831 Breath-by-breath delivered dose comparison from three anti-static valved holding chambers with facemasks under simulated pediatric breathing conditions
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Face masks serve as a patient-device interface to facilitate drug delivery from a pressurized metered dose inhaler (pMDI) with an attached valved holding chamber (VHC), and are capable of significantly affecting inhalation drug therapy. A novel horizontal test rig designed for the evaluation of facemask performance under simulated conditions was used to measure delivered dose from ProAir HFA pMDIs (108 µg albuterol sulfate/actuation, Teva Speciality Pharmaceuticals). Three brands of VHC-facemask systems were tested: preproduction OpTiChamber Diamond (Diamond) VHCs with preproduction LiteTouch facemasks (Philips Respironics), AeroChamber Plus Z Stat (Z Stat) VHCs with ComfortSeal facemasks (Monaghan Medical Corp.), and Vortex VHCs with Spinner Duck facemasks (PARi GmbH).

A face replica of a four-year-old child, with a replaceable aerosol filter in the “mouth”, was connected to a breathing simulator (ASL 5000; IngMar Medical Ltd) to simulate a pediatric breathing pattern (Vt=155 mL, f=25 bpm I:E=2:3). Each VHC-facemask system was naturally positioned against the face replica with a constant applied force supplied by a mass of 1.9 kg. Albuterol sulfate was quantified using HPLC after 1, 2, 4 and 8 “breaths” following pMDI actuation.

Table 1. Mean dose recovered on filter (% of nominal dose)

<table>
<thead>
<tr>
<th>System</th>
<th>Delivery System</th>
<th>Z-Stat/ComfortSeal</th>
<th>Vortex/Spinner Duck</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diamond-LiteTouch</td>
<td>49</td>
<td>4.9</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>26</td>
<td>1.4</td>
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<td>34</td>
<td>9.3</td>
</tr>
</tbody>
</table>

The delivered dose using the Diamond-LiteTouch system, after 1 breath, was significantly higher than the delivered dose using the Z Stat-ComfortSeal or the Vortex-Spinner Duck system after 8 breaths (p < 0.01).
4859  
Physiology is a better predictor of mortality than HRCT findings in patients with fibrotic idiopathic interstitial pneumonia.  
Federica Novellini1,2, Laura Tavani1, Federica Martino1, Stella Cini1, Lorenzo Melosini2, Chiara Romeo1, Fabio Falaschi3, Stefano Solfànnelli3, Alessandro Celi3, Pierluigi Paggiaro1,1, Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy; 2Radiology Department, University of Pisa, Pisa, Italy  
Background: Prognosis of fibrotic idiopathic interstitial pneumonia (IPF) is influenced not only by the histologic pattern observed in lung biopsy but also by high resolution chest tomography (HRCT) and pulmonary function findings.  
Aims: To evaluate if functional parameters are better predictors of mortality that HRCT findings in patients with fibrotic IPF.  
Methods: We studied 43 patients with fibrotic IPF during a follow-up of 37.2±31.7 months after diagnosis. Baseline HRCT was evaluated for different abnormalities: honeycombing (HC), reticulation, ground-glass, bronchiectasis and total fibrosis score. Pulmonary function was assessed as baseline FVC and change of FVC after 6 months of follow-up (less or more 10%).  
Results: DI, using the dots for HRCT scores, a cut-off of 10% in the HC score differentiated patients with different survival (5-yrs survival 41% vs 90%, p=0.04). Patients with HC > 10% had a longer duration of symptoms (p=0.04), a lower baseline DLCO (% of predicted, p=0.006) and higher fibrotic and bronchiectasis score (respectively, p=0.04 and p=0.001) than the other patients. A baseline FVC < 76% (median value) and a worsening FVC at 6 months (vs stable-improved) were associated with lower survival (baseline FVC: 5-yrs survival 57% vs 78%, p=0.03; FVC change: 21% vs 75%, p=0.005). In a multivariate logistic analysis, taking in consideration clinical, radiological and functional findings, only baseline FVC and FVC change resulted still significant predictors of mortality.  
Conclusion: Functional findings are more important prognostic factors of mortality than HRCT parameters in patients with fibrotic IPF.  
4860  
Six-minute-walk test: Desaturation index in diffuse parenchymal lung disease  
Dina Visca, Angelo De Lauretis, Giuliana Pasqueto, Giuseppina Gioské, Smargiassi Andrea, Riccardo Inchingolo, Francesco Macagno, Giuseppe Maria Corbo, Salvatore Valente. Respiratory Medicine, Internal Medicine, Rome, Italy  
Six minute walk test (6MWT) is widely used in the functional evaluation of diffuse parenchymal lung diseases (DPLD). To date, distance walked is the most studied 6MWT parameter.  
We focused our study on desaturation index (DI) in 6MWT. We retrospectively evaluated serial lung functions of 59 consecutive DPLD patients: 28 idiopathic interstitial pneumonia (IPF), 11 connective tissue disease (CTD), 13 sarcoidosis and 7 other DPLD. DI was calculated as the ratio between the area above the curve, which was created using each peripheral oxygen saturation (SpO2) value obtained every 2 seconds, and the distance walked.  
Composite physiologic index (CPI) was used to assess disease severity. Disease progression (“time to irreversible decline” in either FVC levels of 10% from baseline or DLCO levels of 15% from baseline) was quantified from the date of the first 6MWT available, by using proportional hazards analysis. Of the 59 patients, 38 were females, mean age was 66.3 (±11.8 SD), mean FVC was 90% predicted (±24) and mean DLCO was 55% (±24). Median length of follow up was 24.7 months.  
Among 6MWT parameters, only DI (p=0.02), lowest SpO2 (p=0.001) and SpO2 at 1 minute of recovery (p=0.02) significantly differed between IPF and sarcoidosis. DI showed more correlations with other physiologic variables than distance walked: the strongest one was with DLCO (r=-0.53, p=0.0001). On multivariate analysis, the need for invasive or non invasive ventilation (OR=35; [95% IC: 5-255]), the type of ILD (IPF vs Miscellaneous) (OR=22; [95% IC: 1.4-147]), and high-dose steroids during ICU stay (OR=0.19; [95% IC: 0.04-0.99]) were found to be independent determinants of in-hospital mortality.  
Conclusion: This study highlights the poor prognosis of IPF in ICU particularly if mechanical ventilation is required. DI-ILD and Miscellaneous with comparable severity criteria have a better prognosis than IPF: High-dose steroids appear as a protective factor whatever the type of ILD.  
4861  
Abnormal pulmonary arterial remodelling in patients with combined pulmonary fibrosis emphysema (CPE) and idiopathic pulmonary fibrosis (IPF)  
Elisabetta Balestrieri1, Francesca Lunardi1, Emanuela Rossi1, Nazarena Nannini1, Giuseppe Marulli1, Monica Loy1, Federico Rea1, Fiorella Calabrese2, 1Department of Cardiac, Thoracic and Vascular Science, University of Padova, Padova, Italy; 2Department of Diagnostic Medical Sciences and Special Therapies, University of Padova, Padova, Italy  
CPE is a syndrome with distinct clinical, functional and radiological characteristics. Recent works have demonstrated the impact of pulmonary hypertension (PH) on worse survival but little is known about the morphological and molecular substrates. The aim of our study was to evaluate the arterial remodelling and expression of transforming growth factor beta (TGF-β) in the lungs of patients with CPE compared to IPF without PH. The study was performed on lung samples or native lungs (2007-2010 recruitment period): 7 CPE patients (mean age 59±5.8 yrs), 15 IPF patients (mean age 53±10yrs) and 5 non-implanted donors (mean age 30±10yrs) as a normal control group. In all cases morphometry was used to measure arterial intimal, medial, and total thickening and immunohistochemical evaluation of TGF-β was quantified in macrophages and alveolar epithelial cells. In CPEF, FEV1%pred and FVC%pred were significantly less reduced than in IPF (p=0.004 and p=0.003, respectively), while DLCO%pred was similar. Initial and total thickening were significantly increased in CPEF than IPF (p=0.004 and p=0.03, respectively). A trend of increased alveolar TGF-β expression was detected in CPEF compared to IPF (p=0.07) while its expression in macrophages was similar. As expected, arterial remodelling and TGF-β expression were significantly increased in both IPF (p=0.001; p=0.001 respectively) and CPEF (p=0.004; p=0.003, respectively) compared to controls. In conclusion, our study demonstrated that lungs with CPEF display significant arterial remodelling which may represent pathological substrate for the increased occurrence of PH.  
4862  
Outcome of patients with interstitial lung disease admitted into ICU  
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Background: Limited data are available on the clinical course of patients with Interstitial Lung Disease (ILD) and acute respiratory failure requiring admission to ICU.  
Objectives: To investigate the outcome of patients with ILD and acute respiratory failure with special attention to Idiopathic Pulmonary Fibrosis (IPF) or Drug-induced ILD (DI-ILD).  
Methods: Retrospective identification of patients with ILD admitted into ICU between 1993 and 2009. Primary end-point was in-hospital mortality.  
Results: 72 subjects could be included, divided into 3 groups: IPF, n=28; DI-ILD, n=20 and Miscellaneous, n=24. The in-hospital mortality rates were 68, 40 and 25% for IPF; DI-ILD and Miscellaneous, respectively (p=0.008) and reached 100, 64 and 60%, respectively, in those receiving mechanical ventilation (p=0.007).  
On multivariate analysis, the need for invasive or non invasive ventilation (OR=35; [95% IC: 5-255]), the type of ILD (IPF vs Miscellaneous) (OR=22; [95% IC: 1.4-147]), and high-dose steroids during ICU stay (OR=0.19; [95% IC: 0.04-0.99]) were found to be independent determinants of in-hospital mortality.  
Conclusion: This study highlights the poor prognosis of IPF in ICU particularly if mechanical ventilation is required. DI-ILD and Miscellaneous with comparable severity criteria have a better prognosis than IPF: High-dose steroids appear as a protective factor whatever the type of ILD.  
4863  
The King's brief intestinal lung disease quality of life questionnaire (K-BILD) for patients with IPF and other ILDs  
Amit S. Patel1, Richard Siegert2, Kate Brigland1, Sabrina Bhajwah3, Sujal R. Desai2, Aihol U. Wells2, Irene J. Higginson 1, Surinder S. Birring 1, 1Department of Palliative Care, Policy & Rehabilitation, Cicely Saunders Institute, King’s College London, London, United Kingdom; 2Department of Palliative Care, Policy & Rehabilitation, Cicely Saunders Institute, King’s College London, London, United Kingdom; 3Cardiac, Thoracic and Vascular Medicine, University of Oxford, Oxford, United Kingdom  
We set out to develop a brief ILD specific health related quality of life (HRQOL) questionnaire for patients with idiopathic pulmonary fibrosis (IPF) and other ILDs. Items were generated from patient interviews (n=10), literature review and a multi-disciplinary team meeting. A preliminary questionnaire consisting of 71 items and a 7 point Likert response scale was tested in 173 patients (49 IPF). The following items were removed: 1) floor effect: >60% of participants responded
low and generally similar in both treatments, except for visual symptoms during scores and rescue medication usage (all P > 0.05). Ivabradine produced significantly lower mean HR than placebo in all rate (PEFR), symptoms, rescue medication consumption and adverse events (AEs).

Methods: 161 consecutive patients discussed at the ILD MDT meeting at University Hospital of South Manchester were analysed.

Results: In 69 of 161 cases the MDT agreed with the diagnosis of the referring physician. In 67 of 161 cases a single ILD label different to that of the referring centre was given, and in 25 of 161 cases the ILD delivered a differential diagnosis only. Of 67 patients referred with definite IPF only 40 patients (60%) kept their label of IPF; the remaining 27 patients received a different diagnosis, predominantly non-specific interstitial pneumonias (NSIP). At time of follow (3-6 years after MDT discussion) 52% of patients who kept their IPF diagnosis were alive versus 78% of patients alive where a pre-MDT diagnosis of IPF was changed to a more favourable diagnosis, p < 0.05.

Conclusion: This data is the largest ILD MDT cohort thus far reported and is the first report to clearly link an MDT-based change in diagnosis from IPF to NSIP translating into documented improved survival.

503. COPD: integrated care and rehabilitation

Late-breaking abstract: HR-lowering efficacy and respiratory safety of ivabradine in patients with obstructive airway disease

Sebastian Majewski1, Sebastian Slomka2, Ewa Wyderkiewicz-Zielinska1, Lisa Spencer2, Matthew Bartels2, Neil Schluger1, Frances Brogan1, Patricia Jellen1, Byron Thomashow1, Steven Kauw1.

503. COPD: integrated care and rehabilitation

Late-breaking abstract: Sildenafil for chronic obstructive pulmonary disease: A randomized crossover trial

David Ledder1, Neal Schluger1, Frances Bogan1, Patricia Jellen1, Byron Thomashow1, Steven Kauw1.

Introduction: Idiopathic pulmonary fibrosis (IPF), the commonest of the idiopathic interstitial pneumonias, is increasing in incidence/prevalence. Diagnosis can be challenging due to a number of interstitial lung disease with overlapping clinical, radiological or pathological features. Recent guidelines (British Thoracic Society) emphasise the need for multidisciplinary team-based diagnosis, but little published guidance is available to support this recommendation.

Methods: 161 consecutive patients discussed at the ILD MDT meeting at University Hospital of South Manchester were analysed.

Results: In 69 of 161 cases the MDT agreed with the diagnosis of the referring physician. In 67 of 161 cases a single ILD label different to that of the referring centre was given, and in 25 of 161 cases the ILD delivered a differential diagnosis only. Of 67 patients referred with definite IPF only 40 patients (60%) kept their label of IPF; the remaining 27 patients received a different diagnosis, predominantly non-specific interstitial pneumonias (NSIP). At time of follow (3-6 years after MDT discussion) 52% of patients who kept their IPF diagnosis were alive versus 78% of patients alive where a pre-MDT diagnosis of IPF was changed to a more favourable diagnosis, p < 0.05.

Conclusion: This data is the largest ILD MDT cohort thus far reported and is the first report to clearly link an MDT-based change in diagnosis from IPF to NSIP translating into documented improved survival.

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Methods: 161 consecutive patients discussed at the ILD MDT meeting at University Hospital of South Manchester were analysed.

Results: In 69 of 161 cases the MDT agreed with the diagnosis of the referring physician. In 67 of 161 cases a single ILD label different to that of the referring centre was given, and in 25 of 161 cases the ILD delivered a differential diagnosis only. Of 67 patients referred with definite IPF only 40 patients (60%) kept their label of IPF; the remaining 27 patients received a different diagnosis, predominantly non-specific interstitial pneumonias (NSIP). At time of follow (3-6 years after MDT discussion) 52% of patients who kept their IPF diagnosis were alive versus 78% of patients alive where a pre-MDT diagnosis of IPF was changed to a more favourable diagnosis, p < 0.05.

Conclusion: This data is the largest ILD MDT cohort thus far reported and is the first report to clearly link an MDT-based change in diagnosis from IPF to NSIP translating into documented improved survival.
Results: We identified 26,516 individuals with COPD (59% female, mean age 61±13 years) of whom 80% contributed adherence data. Adherence rates (mMPR±s.D. number contributing) were 0.62±0.34, n=13173 for anticholinergics (AChI), 0.61±0.32, n=2018 for inhaled corticosteroids (ICS), and 0.66±0.29, n=5336 for long-acting beta-agonists (LABA). The relative risk for subsequent AE based on a 0.20 difference in mMPR at the start of follow-up was 0.86 (95% CI 0.80 to 0.94) for ICS, 0.91 (0.84 to 1.00) for LABA, and 0.89 (0.84 to 0.93) for AChI.

Conclusions: Better adherence to any of the major classes of inhaled controller therapeutics reduced the risk of subsequent AE-COPD.

Funding: Investigator Initiated Grant, Novartis Pharmaceuticals Corporation.

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Provision of nonpharmacological treatment options for COPD patients in 13 European countries: Results from the European COPD audit

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Background: Evidence from the literature suggests that nonpharmacological treatment for COPD patients improve the outcome of this disease. To explore the provision of non invasive ventilation (INV), early supported discharge programs, and thoracic surgery, a cross-sectional study, date from European COPD audit study was evaluated in 258 hospitals from 13 European countries

Study design: In an observational study, all participating hospitals collected data on the organisation of care for COPD admissions. Preliminary results of 258 (132 general/153 teaching/university) hospitals out of 450 participating centres of the ongoing study will be presented.

Results: Although the majority of centers offer noninvasive (ICU and/or HCU) High dependency care units available for decompensated COPD patients, the capacity for eligible patients is only close to 60%. In addition, supported discharge as well as pulmonary rehabilitation programs are provided in less than 50% of cases.

Conclusions: Contrary to international recommendations, participating European centers in the COPD audit lack sufficient availability for non invasive ventilation; in addition, neither rehabilitation, nor early supported discharge programs are sufficiently available. University hospitals are not superior to general hospitals.

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Integated care intervention prevents hospitalisations for exacerbations and reduces the disease costs in COPD patients

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Introduction: Efficacy of interventions aimed at preventing hospitalisations due to exacerbations in clinically stable COPD patients is controversial.

Objectives: To evaluate usefulness of integrated care intervention (ICI) on hospital admission for exacerbations and disease costs in COPD patients.

Methods: This prospective study was carried out in 208 COPD patients recruited by general practitioners between January 2009 and December 2009 in Massa-Carrara sanitary district.

The interventions included individually tailored care plan following GOLD guide- lines shared among the chest physician, nurse team and general practitioner, educational program on self-management of the disease, treatment supervision during scheduled visits, home visits by specialised nurses.

Results: 105 patients completed 12 months of follow-up, stratified at stage 1 (n.11), stage 2 (n.47), stage 3 (n.34), stage 4 (n.13) using the GOLD classification. Twelve months of ICI decreased the mean number of hospitalisations (0.54±1.1 versus 0.82±1.1; p<0.05), reduced the percentage of hospitalised patients (27% versus 50% respectively) compared to the previous year. Gold 3 and 4 stages showed the highest reduction in hospitalisation rate. Drug-acquisition costs sign-

ificantly increased (average difference in means ± 256 €) while the mean total disease cost per patients decreased (-201 €) after ICI.

Conclusions: The study demonstrates that a standardised ICI based on share-care intervention between primary care team and hospital team effectively prevents hospitalisations for exacerbations and decreases the total disease cost in COPD patients.

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Establishment of an integrated clinical network and comprehensive data warehouse for the conduct of comparative effectiveness research in COPD

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Background: Chronic obstructive pulmonary disease (COPD) affects many mil-

lions worldwide and is increasing in incidence, morbidity, and mortality. Efficacy trials can guide COPD care, but an infrastructure for comparative effectiveness research (CER) across diverse settings is needed to more fully evaluate commonly used therapies in clinical practice.

Methods: We created an inter-disciplinary and multi-institutional network for CER named COPD Outcomes-based Network for Clinical Effectiveness and Research (CER). We developed a platform for comprehensive interoperable clinical data upload and synthesis across diverse outpatient and hospital practice settings to create a comprehensive COPD data warehouse (COPD DataHub) and have begun populating it thru inclusion pathways designed to maximize identification of COPD patients from 2006 through 2008.

Results: The COPD DataHub was designed to be flexible to incorporate data from seven varied health care settings including university-affiliated medical centers, a community medical center, a health maintenance organization and a government-operated veteran medical center. It includes a total of 146,240 unique patients, 58.3% female at non-veteran sites, whites 68.4%, blacks 14.3% and other races 17.3%, average patient age 61.8 years (S.D. 13.5).

Conclusions: We demonstrated the feasibility of developing a rich CER data reposi-

itory by linking COPD patients across diverse sites. CONCERT has successfully created a multi-institutional platform to pursue observational CER studies and identify patients with COPD for enrollment into prospective pragmatic clinical trials.

4872

Lack of oximeters in primary care risks increasing the mortality from COPD

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The ERS and ATS (2005), GOLD (2010), NICE (2010) guidelines for COPD recom-

mend long term oxygen therapy (LTOT) in hypoxic patients. LTOT improves the mortality of these patients. NICE recommends that patients with oxygen satu-
rations which are <92% on breathing air should be assessed for LTOT. In order to do this these patients must be identified with pulse oximetry.

Aims and methods: This study was performed in 2010 to examine the availability of pulse oximetry in GP surgeries and the views of GPs to pulse oximetry by post or questionnaire in all 67 practices who serve this hospital.

Results: 60 practices (89%) responded to the questionnaire. Of these 40 (66%) had ≥ 1 pulse oximeters. 24 (40%) had only one oximeter, usually shared between doctors and nurses. 20 (33%) had no oximeter. 64 (23%) stated they would like an oximeter whilst 4 (6.6%) thought an oximeter was not necessary. The main reason given for not having an oximeter was financial.

Conclusions: 33% of GP practices do not have a pulse oximeter. 40% have only one oximeter, which was usually shared between doctors and nurses. Lack of oximeters could lead to referral to secondary care just to have pulse oximetry measured. Lack of finance was the major reason given for not having an oximeter.
but oximeters are now cheap and one referral into secondary care is approximately equivalent to the cost of an oximeter. This study suggests that hypoxia patients with COPD will not be identified early and therefore not treated with LTOT. This will mean that their life expectancy will be reduced. The identification of hypoxia patients in primary care must be urgently addressed by increasing the number of oximeters.

504. Innovative methods in clinical physiology

4873
Late-breaking abstract: Lung recruitment in normal and emphysematous rats during methacholine challenge
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Elastase-induced emphysema in rodents is characterized by enlarged alveoli and decreased lung elastance but generally no change in airway resistance. We studied airway and tissue mechanics and recruitment in rats before and during constrictor challenge. Sprague-Dawley rats were treated by intratracheal instillation of 50 U porcine pancreatic elastase (PPE, n=6). Three weeks later, these animals and 6 controls (C) were anesthetized, tracheotomized and mechanically ventilated. From low-frequency impedance (Zrs), tissue damping (G), elastance (H) and hysteresivity (ηPH) were estimated. The lungs were degassed in vivo with oxygen breathing (10 min) and tracheal occlusion (10 s), and then reinfated to 35 hPa, while the pressure-volume (PV) relationship and intratracheal crackle sound (Cra) were recorded. Measurements of Zrs, PV and Cra were repeated during i.v. infusion of methacholine (Mch) at 64 μg/kg/min. RN was not different between groups PPE and C at baseline (44.4±4 vs 46±10 hPa/l, p>0.05) and during challenge (165±14 vs 176±37 hPa/l). G and H, respectively, were significantly lower in the PPE group compared to the controls (613±57 vs 839±165 hPa/l, and 227.3±301 vs 3033±385 hPa/l, although their elevations due to Mch were similar: 13% vs 17%, 3% vs 14%, and 24.1% vs 25.2% for H). Whereas cumulative crackle intensity reached 80% at similar P levels in both groups, the recruited volume was more reduced during challenge (39 vs -16% in the PPE group. In a number of rats, airway resistance and recruitment remained unaffected, the tissue damage was associated with an enhanced tissue constrictor response following elastase treatment. Supported by grants OTKA 66700 and NIH HL090757.

4874
The measurement of absolute lung volume without plethysmography
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A basic and important component of pulmonary function testing is determination of absolute lung volumes, including total lung capacity (TLC). However this involves the use of equipment such as a Body Plethysmograph (BP) that is unsuited to routine office practice. To determine TLC, we report here a new mechanical approach – the Partial Volume Method, PVM – that requires neither BP, gas dilution, nor thoracic imaging, yet is simple, compact, rapid, inexpensive, and accurate.

With cheeks supported, the subject breathes through a flow interruption valve downstream of a parallel chamber of known volume. As a result of respiratory system inertia, respiratory flow continues undiminished for a very short time (<15 ms) after valve closure. This continuing flow compresses chamber gas in a manner inferable from Boyle’s law, and used to deduce instantaneous absolute thoracic gas volume. In 106 healthy adults (40 women, 30±11.5 y, 22.8±1.4 BMI, 66 men, 29±10.2y, 24.0±3.1 BMI), TLC was measured using both PVM and standard plethysmography (ZAN 500, nSpire, Inc). For the combined group, TLC_PVM = 0.981 TLC_PLETH, R^2 = 0.87. R^2 = 0.943 (Pearson, CE 0.961-0.918. The coefficient of variation (CV) for repeated PVM trials was 3.44%. Together, these results establish a new method for accurate, rapid, and reproducible determination of TLC in healthy subjects with minimal subject cooperation. This work was sponsored by PulmOne Ltd., Ra’anana, Israel.

4875
Influence of end-expiratory level and tidal volume on ventilation distribution
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Background: Our understanding of regional filling of the lung and regional ventilation distribution (VD) is based on studies using radio labelled tracer gases. We aimed to investigate whether these results can be reproduced and differences in regional filling and spatial VD can be detected with electrical impedance tomography (EIT) in adults at different end-expiratory levels (EEL) and tidal volumes (VT).

Methods: EIT measurements were performed in 10 healthy adults in right lateral position. Five different EEL with four different VT at each EEL were tested in random order, resulting in 19 combinations. There were no measurements for the combination of the highest EEL highest VT as it was not possible to achieve this breathing pattern. EEL and VT were controlled by visual feedback. The fraction of ventilation directed to the right lung (VRight) and the rate of regional filling (right lung vs. total lung) were analysed.

Results: Visual feedback resulted in distinct differences in EEL and VRight increased with increasing EEL and was <0.5 (more air directed to the left lung) only at the lowest EEL (p<0.05). With low EEL the filling of the right lung during the initial phase of the inspiration was slower (p<0.05) and the filling the lungs became more even with increasing EEL. With increasing VRight increased significantly (p<0.05) and the filling characteristics changed towards more uneven ventilation.

Conclusion: The effect of different EEL and VRight spatial and temporal VD during spontaneous tidal breathing in right lateral position can be assessed by EIT. Our results are in line with previous studies and suggest that the effect of EEL on ventilation distribution is greater than the effect of VRight.

4876
K-edge subtraction (KES) synchrotron imaging allows quantitative measurement of regional aerosol deposition, lung ventilation and airway morphology in rabbit
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Rationale: The simultaneous measurement of regional lung ventilation, aerosol deposition and the anatomic configuration of airways are crucial for the better understanding of the determinants of aerosol deposition heterogeneity. However, no single imaging modality currently allows the acquisition of all such data simultaneously. The goal of this study was to test the feasibility of KES imaging to this end.

Methods: We used KES synchrotron radiation imaging (AIRCCM, 2009;180:296–303) to quantify regional lung ventilation, and the deposition of iodine (isopropyl 88 mg/ml in NaCl 0.9%), delivered using an ultrasonic nebulizer (mass median aerodynamic diameter: 2.6±0.1 μm), in a healthy anesthetized, and mechanically ventilated rabbit (2.8 kg) in upright position. Regional ventilation images were obtained in 4 axial slices during inspiration of O2/Ne in O2. Regional deposition images were obtained in 45 contiguous slices after 0.5, 10, 15 and 20 minutes of nebulization.

Results: See figure. Aerosol deposition showed significant spatial heterogeneity in normal lung. Inset: 3D rendering of central conducting airways (dark) and iodine (medium) and parenchyma (light grey).
Conclusions: These data demonstrate the feasibility of K-edge subtraction imaging for the quantitative measurement of regional aerosol deposition, lung ventilation and airway morphology in vivo.

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Chest wall kinematics in patients with osteogenesis imperfecta (OI)
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In Osteogenesis imperfecta (OI), an inherited connective tissue disorder characterized by brittle bones and significant chest wall (CW) deformities, pulmonary complications are the principal cause of death. In order to study how OI affects chest wall function, we studied 7 patients with severe form type III (OI3), 15 with moderate form type IV (OI4) and 26 healthy subjects (CTR). Breathing pattern, regional CW volume changes and thoracoabdominal asynchronies at rest in seated and supine position were measured by opto-electronic plethysmography. Rib cage deformities were assessed from OEP markers by computing the angle of the sternum (a) on the transversal plane. In both positions, minute ventilation was lower in OI than CTR because of lower tidal volume (p<0.01). Abdominal tidal volume in OI3 was higher and associated to low pulmonary rib cage contribution which was even negatvie (inspiratory paradoxical inward motion) in supine (figure). OI3 showed reduced a (161.6±17.5°; 173.6±10.5°; 181.7±12.9°) in OI3, OI4 and CTR, p<0.01 and higher thoracoabdominal asynchrony (labeled breathing index=1.32±0.4; 1.03±0.03; 1.02±0.02 in OI3, OI4 and CTR, p<0.001).

In conclusion, OI3 is characterized by rib cage deformities (pectus carinatum) which alters CW function during breathing. The reduced or paradoxical rib cage motion during inspiration is compensated by an increased action of the diaphragm at rest, associated with large thoracoabdominal asynchrony.

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Diaphragm fatigue in self-paced running exercise of different durations
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Introduction: Diaphragm fatigue (DF) was shown to develop during high intensity constant load exercise (CLE) above 85% of maximal oxygen consumption (VO2max). CLE does, however, not appropriately reflect field trial conditions where exercise intensity is regulated by complex feedback and feedforward mechanisms, possibly aiming to reduce/prevent DF. Therefore, the development of DF was assessed in 11 well-trained athletes (age=31.4±4 yrs, VO2max=66.7±4.6 ml/min/kg) in 15 and 30min running time trials (TT). We hypothesized that DF would be larger in the 30TT where more time is spent above 85% VO2max.

Methods: Before and 4min after completion of the TTs, esophageal and gastric pressures were assessed to calculate transdiaphragmatic twitch pressures (Pdi,tw) during cervical magnetic stimulation.

Results: All three developed DF (Pdi,tw reduction, ΔPdi,tw >10%) in the 15TT and 7/11 subjects in the 30TT. On average, ΔPdi,tw was 23 ±6.5 (15TT) and 18.5±12.1 (30TT; p=0.13). Mean exercise intensities were 89.4±3.5 (15TT) and 80.6±3.7% VO2max (30TT; p=0.07) with similar mean durations above 85% VO2max (11±3.2min; range: 7-14min; 15TT) and (16.2±6.7min; 1-28min; 30TT; p=0.19).

The individual between-TT difference in ΔPdi,tw did not correlate with the difference in time spent above 85% VO2max (R2=0.20) but correlated with the difference in average exercise intensity above 85% VO2max (R2=0.49; p<0.02).

Conclusion: In TT-conditions, the degree of DF is not related to the duration spent above 85% VO2max but it is related to the exercise intensity when exercising above the 85% VO2max-threshold.

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Ultrasound measurement of quadriceps wasting in patients with GOLD stage II COPD and its relationship to physical activity
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Introduction: Ultrasound measurement of rectus femoris cross-sectional area (USRFCSA) is a radiation-free measure of muscle bulk that relates to quadriceps strength.1 A recent study reported that a significant proportion of GOLD stage II patients have quadriceps weakness.2 We hypothesised that quadriceps wasting, measured by USRFCSA, would be observed in GOLD stage II patients and would correlate with daily physical activity levels.

Methods: USRFCSA and quadriceps maximum voluntary contraction (QVMC) were measured as described by Seymour et al.1 Physical activity was recorded for six consecutive days using a multisensor biaxial accelerometer, SenseWear Pro Armband3,4. Fat free mass (FFM) was estimated using bioelectrical impedance and a disease specific regression equation.

Results: We studied 100 patients with stable COPD, (GOLD stage II-33%, III-34%, IV-33%), mean (SD) age 65 (9) years, 57% male and 23 age-matched healthy controls. USRFCSA was significantly reduced (517mm2 vs 626mm2; p=0.005) in Stage II patients compared to controls. USRFCSA was also significantly reduced in stage III (500mm2; p=0.006) and IV (522mm2; p=0.007) disease. Using a stepwise regression model in all patients, FEV1/FVC predicted and USRFCSA, but not FFM index and QVMC, correlated with daily physical activity (steps) (R2=0.4, p<0.001).

Conclusion: USRFCSA is reduced in GOLD stage II COPD and is related to daily physical activity. USRFCSA provides a bedside method for identifying quadriceps muscle loss in less severe disease and may guide the application of pulmonary rehabilitation in these patients.

is not sufficiently high to replace PS0 in the evaluation of individual patients with suspected disturbances of hemoglobin oxygen affinity.

506. Asthma mechanisms

4885 Degree of bronchial hyperresponsiveness (BHR) and new onset of respiratory diseases 9 years later

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In the European Community Respiratory Health Survey, 10933 subjects aged 20-44 years (29 countries, 14 countries) had both a baseline (1991/3) and a follow-up (2002/4) evaluation. The degree of baseline BHR was defined in 836 (77%) subjects as absent (PD20=1 mg) (n=6852); and low (PD20, mg: (0.5-1]), medium (0.15-0.5) or high (0-0.15), based on PD20 distribution tertiles. Two-level logistic regression models (2nd level, center) were used to analyze the association between BHR degree and new onset of nasal allergies (allergic rhinitis, AR) and COPD (pre-bronchodilator FEV/FVC=0.70) in non-asthmatic subjects; current asthma and symptoms (wheeze, chest tightness, dyspnea at rest/after exercise/at night), and new onset of asthma symptoms in subjects who were free from the respective outcomes at baseline. The analyses were adjusted for gender, age, height, education, pack-years, FEV1 and atopy (IgE >0.35 kU/L to cat, mite, grass or grass pollen). An increased BHR degree was associated with an increased risk of developing COPD, asthma and asthma-like symptoms 9 years later (see table).

These preliminary analyses support the interest for BHR degree as a predictor of several adult-onset respiratory diseases.

4886 Chronic rhinosinusitis and airway inflammation in new onset asthma in adults

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Rationale: In severe asthma, chronic rhinosinusitis (CRS) is associated with increased sputum eosinophils [Brooke, JACT 2002]. Many adults with severe asthma have the onset of their disease in adulthood. We hypothesized that the relationship between the severity of CRS and inflammation in the lower airways already exists in the early stages of adult-onset asthma.

Aim: To investigate the relationship between CRS and airway inflammation in adults with new onset asthma.

Methods: Ninety-eight adults (>18yr) with a physician diagnosis of recent (>1yr) onset asthma (age 48 (41.6yr), pH FEV1 99 (±8.8)/p% 66% female, 43% atopic, 20% steroid naive) were recruited. Diagnosis was based on reversibility in FEV1 ≥12%pred and/or PD20 methacholine < 8 mg/ml. Patients with COPD were excluded.

CT-scanning was performed and blindly scored for sinonasal mucosal thickness using LMK score [Land Rhinology 1993]. Sputum was induced and processed, exhaled nitric oxide (FeNO), pH FEV1 and methacholine challenge were performed and venous blood was taken. LMK scores were related to sputum cell counts, FeNO and lung function and blood using Spearman correlation coefficient. The analyses were adjusted for gender, age, atopy, history of allergic rhinitis, history of allergic asthma, BMI, current smoking, and pack-years.

Results: There was a significantly positive correlation between CT scores and eosinophils in induced sputum (R=0.73, p<0.001) and peripheral blood (R=0.73, p<0.001) and level of FeNO (R=0.38, p<0.05). No correlation was found between CT-scan scores and pH FEV1. Predictors were PD20 (p=0.75) and PD20 methacholine (p=0.15).

Conclusion: In adults with recent onset asthma, the degree of CRS and lower airways inflammation are closely related. This implies that patients with recent onset asthma should be checked and treated for upper airways disease, if necessary.

4887 Association between airway hyperresponsiveness, obesity, and lipoproteins in a young Danish cohort

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Rationale: Epidemiological data have linked obesity with an increased risk of asthma in the community. However, the mechanisms responsible for this relationship remain unknown. The present study investigated the association between airway hyperresponsiveness to methacholine (AHR) and body mass index (BMI) and plasma lipoproteins (LDL, HDL and total cholesterol).

Methods: Associations between AHR, BMI and plasma lipoproteins were assessed in a population-based cohort at ages 14 and 20 years. Main results: In unadjusted analyses, higher LDL cholesterol levels at age 14 were associated with AHR to methacholine at age 20 in both sexes (p<0.05). HDL, LDL/HDL ratio and total cholesterol were not associated with AHR. In a multiple regression analysis adjusted for sex, lung function, smoking and asthma, only higher levels of BMI at age 14 were significantly associated with increased AHR at age 20 years, while neither LDL, HDL, LDL/HDL ratio nor total cholesterol were significantly associated with AHR to methacholine.

Conclusions: We confirmed that there is a strong association between BMI and AHR to methacholine in young people. This association seems to be independent of the plasma lipoprotein levels and we did not find an independent association between levels of lipoproteins and AHR.

4888 Effect of vitamin D treatment on antimicrobial peptides in asthma patients and healthy controls

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Vitamin D deficiency has been linked to asthma because of the proposed role of vitamin D in inflammation control and host defense against infection. Antimicrobial peptides (AMPs) are effector molecules of the innate immune system, and their expression may be decreased by allergic inflammation. Vitamin D increases expression of AMP in vitro, but its effects on AMPs levels in asthma patients are unknown. Hypothesis: AMP levels in nasal secretions of patients with allergic asthma are lower than in controls and can be restored by vitamin D substitution. Methods and results: 20 allergic asthma patients and 20 controls (18-45 yrs) were included. The influence of allergic asthma on AMPs was assessed in a case control design, and the effect of 7 days daily oral treatment with 2 mg 1,25(OH)2D3 active vitamin D (calcitriol) on AMPs was assessed in a placebo-controlled cross-over study. The levels of the AMPs HNP1-3 and NGAL were significantly lower in asthmatics, whereas there was a trend for an increase in LL-37 (table 1).

Table 1. Mean AMP in asthma patients and healthy controls.

<table>
<thead>
<tr>
<th>AMP</th>
<th>Asthma Controls</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>HNP1-3 ng/ml</td>
<td>3215</td>
<td>0.023</td>
</tr>
<tr>
<td>LL-37 ng/ml</td>
<td>99</td>
<td>1.34</td>
</tr>
<tr>
<td>NGAL ng/ml</td>
<td>2333</td>
<td>0.007</td>
</tr>
<tr>
<td>SLPI g/ml</td>
<td>893</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Treatment with 1,25(OH)2D3 significantly increased HNP1-3 and there was a trend for an increase in LL-37 and NGAL.
Introduction: Mechanism of BA onset and progression at different ages is still poorly understood and eotaxin in upper airways is a tempting object of investigation into BA pathogenesis.

Methods: We examined 70 patients with asthma. The patients' age ranged from 16 to 74 years. We studied 31 men and 39 women. The control group used was comprised of 30 healthy volunteers with no history of atopic diseases. Were studied 16 to 74 years. Were studied 31 men and 39 women. The control group used was comprised of 30 healthy volunteers with no history of atopic diseases.

Results: A study in patients with asthma was revealed a significant increase in eotaxin mRNA expression (p = 0.045), eotaxin-2 (0.036), MIP-1β (0.003), MIP-1α (0.002) and CXCR2 (0.004) compared with healthy volunteers. At the same time the gene expression in patients with asthma was reduced compared with control. To study the age dynamics of the asthma patients were divided into 4 groups: first group - 16-25 years (n = 14), the second group - 26-39 years (n = 14), the third group - 40–53 years (n = 21) and the fourth group - 54-74 years (n = 21). Eotaxin-2 had wave-like dynamics depending on patients age. MIP-1α was lowest in the second and third groups, and in the first and fourth - significantly decreased. The values of MIP-1β - the lowest in the first group with increasing age became more and peaked in the fourth group. mRNA of CCR1 and CXCR1 was significantly decreased in the second group compared to the first, meanwhile in the third and fourth ones levels of mRNA of both receptors increases depending on the age of the patients.

Conclusion: The state of chemokines and relative receptors gene expression in upper airways reflects age features of BA pathogenesis.

Introduction: Chemoattractants and their receptors mRNA expression in brush-biopsies of nasal polyps in bronchial asthma patients

Methods: We examined 70 patients with asthma. The patients' age ranged from 16 to 74 years. We studied 31 men and 39 women. The control group used was comprised of 30 healthy volunteers with no history of atopic diseases. Were studied 16 to 74 years. Were studied 31 men and 39 women. The control group used was comprised of 30 healthy volunteers with no history of atopic diseases.

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Conclusion: The state of chemokines and relative receptors gene expression in upper airways reflects age features of BA pathogenesis.

Conclusion: Levels of AMPs are lower in nasal secretions in asthmatics, and treatment with active vitamin D increases these levels.

Introduction: Rapamycin inhibits IL-33-induced airway inflammation

Methods: BALB/c mice were treated intranasally with 1 μg IL-33 daily with or without 1 mg/kg rapamycin for 5 days. Airway inflammation was assessed on day 6 by bronchial/ovarian lavage (BAL) cellularity and cytokine analysis.

Results: Intranasal IL-33 induced profound airway inflammation with increased cellular recruitment on BAL consisting mainly of macrophages and eosinophils. Treatment with rapamycin significantly reduced IL-33-mediated cellular recruitment (Figure 1A) and reduced both eosinophil (Figure 1B) and macrophage (Figure 1C) influx into the airway.

Conclusions: Levels of AMPs are lower in nasal secretions in asthmatics, and treatment with active vitamin D increases these levels.

Conclusion: Levels of AMPs are lower in nasal secretions in asthmatics, and treatment with active vitamin D increases these levels.

Article title: Rapamycin inhibits IL-33-induced airway inflammation

Authors: Ananya Mirchandani, Robert Salmond, Foo Liew.

Abstract: Rapamycin was initially described as a macrocidal antibiotic that selectively blocks the mammalian target of rapamycin (mTOR), a serine/threonine kinase involved in inflammation and the associated signalling pathways are incompletely understood. Rapamycin also significantly reduced IL-33-mediated IL-5 and IL-13 production and IL-33-induced IL-6 production.

Conclusions: Levels of AMPs are lower in nasal secretions in asthmatics, and treatment with active vitamin D increases these levels.

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Tuberculosis in special populations

4894 Impact of African immigration on drug resistance to Mycobacterium tuberculosis in Portugal
Carina Gaetan, Carlota dos Santos, Nelson Diogo. Pneumology Department, Pulido Valento Hospital, Lisbon, Portugal

Background: Several works pointed immigration as a risk factor for drug resistance in Western countries. In Portugal immigration is responsible for 13.6% of tuberculosis cases, 75% of those cases being originated from Sub-Saharan African countries.

Aim: To evaluate the role of immigration from African countries in drug resistance to Mycobacterium tuberculosis (Mt) in Portugal.

Methods: Comparative retrospective study between African immigrants (I) and native (N) patients with positive culture to Mt and who realized susceptibility tests, admitted in a Pneumology unit from 2000 to 2010. Clinical-demographic characteristics, aetiopathogenic factors, drug resistance profiles and inhospital outcomes were evaluated.

Results: 1232 patients were enrolled, 240 (18.1%) being immigrants, most of them from Portuguese spoken countries. Statistically significant differences were found on the following variables: drug addition (I: 6.7% vs N: 28.8%); WHO classification; number of previous treatments (I: 0.21 vs N: 0.37); duration of previous treatments (I: 0.88 vs N: 1.83); inhospital mortality (I: 4.2% vs N: 8.5%). The variables with predictive value for resistance in this population were HIV co-infection, number of previous treatments and chronic TB infection. The total incidence of drug resistance was similar in both groups (I: 20.8% vs N: 21.0%), but secondary resistances were less frequent in immigrants (I: 5.4% vs N: 9.7%).

Conclusion: African immigration was not associated with increased prevalence of drug resistance to Mt. These findings can be explained by the reduced access to antituberculosis drugs in Sub-Saharan countries.

4895 Double impact: Difficulties in treating patients with liver diseases from tuberculosis
Hoda Makhlouf 1, Nahed Makhlouf 2, Mohamed Metwally 1, Hebat Alla Rashid 3

Background: Tuberculosis and liver disease are both endemic in many parts of the world. Many anti-TB drugs have hepatotoxic side effects and should be used cautiously during their use in liver disease patients.

Objectives: To assess the frequency and risk factors of anti-TB Drug-Induced Hepatotoxicity (Anti-TB-DIH) among patients with viral hepatitis and liver cirrhosis.

Patients & Methods: This prospective study included 26 TB patients of pulmonary and extrapulmonary TB associated with liver cirrhosis or viral hepatitis in addition to, 46 TB patients without liver disease as controls. All patients were followed up clinically and biochemically before and during their treatment.

Results: Anti-TB-DIH was noticed in 30.8% patients with liver disease (46.2% and 15.4% in liver cirrhosis and viral hepatitis respectively; P=0.089) and in 8.7% of control group (P<0.05 vs liver disease). Anti-TB-DIH developed within 15-60 days from the onset of therapy. Liver functions normalized in 25% of patients with liver disease within 2 weeks from cessation of therapy. By univariate analysis, liver diseased patients with anti-TB-DIH had lower body mass index (P=0.049) and lower serum albumin (P=0.008). Using multivariate regression analysis proved that lower serum albumin was independent predictors of anti-TB-DIH (P=0.018) in liver diseased patients while the presence of other co morbid diseases was the only risk factor in patients without liver disease (P=0.024).

Conclusion: Anti-TB-DIH is common among patients with liver diseases and is more in patients with lower serum albumin while the presence of other co morbid diseases is only risk factor for DIH in TB patients without liver disease.

4896 Hepatitis C virus infection among tuberculosis patients in Sohag
Governorate: Seroprevalence and associated risk factors
Mohamed Badawy 1, Mona Taha 1, Laia Mohamed 1, Ahmed Fathy 1

Chest Department, Clinical Pathology, Public Health Department, Sohag University Hospital, Sohag Faculty of Medicine, Sohag, Egypt

Setting: Tuberculosis (TB) and hepatitis C virus (HCV) infection have emerged as major public health problems in Egypt.

Objective: To determine the prevalence and risk factors for the HCV infection among patients with TB in Sohag.

Material and methods: A cross-sectional study was carried out at Sohag university hospital. Hundred thirty five tuberculosis patients were fulfilled the inclusion criteria. age more than 15 years old, patients with all form of tuberculosis either pulmonary or extra pulmonary. Anti-HCV antibodies were done for all patients. A case-control study was performed to identify risk factors for HCV infection. Cases were defined as patients with TB who were HCV-seropositive, and controls were defined as patients with TB who were HCV-sero-negative.

Results: HCV infection was diagnosed in 21/135 (16.4%). Goa'za smokers (P value 0.01 Odds Ratio 3.75, 95% confidence interval 0.24 – 0.44), history of operation (P value 0.01 ORs 7.67, 95% CI 1.65 – 0.263), blood transfusion (P value 0.004 ORs 7.2, 95% CI 1.103 – 0.362), presence of tattoos (P value 0.03 ORs 3.4, 95% CI 0.168 – 0.338), extra pulmonary tuberculosis (P value 0.004 ORs 3.5, 95% CI 2.341 – 3.384), low serum albumin (P value 0.002 ORs 0.5, 95% CI 0.068 – 0.317) were the main risk factors associated with HCV infection.

Conclusion: Universal screening for HCV infection in TB patients is highly recommended. There is an urgent need to detect HCV infection in high-risk groups to prevent future HCV transmission as well as morbidity and mortality associated with TB.

4897 Detection of active TB among people living with HIV/AIDS and vulnerable population groups (commercial sex workers and injecting drug users)
Alexandra Solovyova 1, Alexander Golubkov 2, Elena Borzunova 2

Conclusion: To increase coverage of preventive TB screening and assess prevalence of TB among vulnerable groups in Tomsk, Russia.
Methods: During 2010, a cohort of 703 persons was identified as a risk group for TB. Screening was conducted twice a year and included basic evaluation of symptoms, PPD (DIASKIN-TEST) and chest fluorography. Evaluation involved qualitative interviews with suspects to detect chronic cough, weight loss, night sweats and hemoptysis and other symptoms of TB. Outreach workers of Tomsk-AntiAIDS Foundation provided field counseling, TB and HIV education, phlebotomy, PPD with further referral to TB Services for medical evaluation. Nutritional support, hygiene packages and accompaniment used as incentives to complete screening.

Results: Out of 703 people at risk screened for TB, 30 suspects were sent for medical examination to TB Services (4.3%). Out of them, 6 were diagnosed with active TB (20.0%), including 2 MDR-TB cases.

Conclusion: Enhanced preventive screening and further medical assessment of TB suspects from vulnerable population resulted in high prevalence of active disease (850/100,000). There is a need to continue and expand coverage of preventive screening for the rest of risk group in Tomsk Oblast.

4898 Tuberculosis screening among intravenous drug users (IDU) in Georgia
Nana Kiria, Medea Gegia, Iagor Kalandadze

The National Tuberculosis Programme, The National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia

Background: IDU is widespread in Georgia and regardless of HIV status it is at increased risk of developing active TB. It is necessary to identify the screening and effectively address the TB cases among IDUs.

Aim: To assess the prevalence of TB among IDUs.

Methodology: Using the data of prospective cohort study: from April 2008 to January 2011 IDUs at harm reduction and VCT sites were screened for TB symptoms using the questionnaire.

TB suspects cases were referred to TB units for further investigation and diagnosis.

Results: 4985 IDUs were screened for TB symptoms, 79 (2%) from them were female and 4906 (98%) - male. Mean age was 33. 81 (1.6%) from the screened IDUs were HIV-positive and 2304 (46%) were diagnosed to have Hepatitis B or C. 436 (8.7%) were defined as TB suspects. They were presented at TB units for further examinations. TB was confirmed in 175 cases, 109 (62%) had pulmonary TB and 66 (38%) – extrapulmonary. The prevalence of TB among IDUs was 3510 per 100,000 which is 26 times greater as compared to TB prevalence in general population.

Conclusions: Given the high risk for TB among IDUs, interventions such as active case finding, is urgently needed to detect TB cases as early as possible and treat them adequately.

4899 Managing tuberculosis in chronic kidney disease: An evaluation of patient treatment regimens
Alexandra Riding 1, Paramita Palchabdhi 1, Parvin Begum 2, Marlies Ostermann 2, Heather Möhr 1

1Department of Respiratory Medicine, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; 2Department of Renal Medicine, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom

Introduction: Balancing side effects against effective tuberculosis (TB) treatment

892s
in Chronic Kidney Disease (CKD) can be difficult leading to variations in management. We reviewed patients with CKD and TB to investigate compliance with new treatment guidelines by the British Thoracic Society.

Methods: Retrospective review of patient case notes with CKD who developed TB between 1994-2010 in a single tertiary hospital. Categories included drug dosage, side effects, treatment duration, respiratory team input and outcome.

Results: We reviewed the notes of 40 patients. 11 had incomplete data. In 73% (52/71) of prescriptions dosing regimens were consistent with BTS guidelines. Errors included over-dosing of Rifater and Isoniazid in 2 patients, and under-dosing of ethambutol in 13 patients. Daily dosing of ethambutol (10/14) and pyrazinamide (10/12) in haemodialysis patients was common and not ideal. Side effects were recorded in 22/29 patients: 3 rifampicin, 5 isoniazid, 3 ethambutol, 4 pyrazinamide, 1 streptomycin and 6 to any/combination drugs. Increased treatment duration (12/29 cases) due to side effects was common. All patients were cured and 23/29 (79%) received specialist respiratory physician input.

Conclusion: Management of TB in CKD patients was variable. Side effects from anti-TB drugs were common, but good, all not patients received respiratory physician input. The new BTS guidelines for drug regimens will hopefully standardise management of CKD patients with TB.

1 BTS Standards for Tuberculosis Care. Guidelines for the prevention and management of Mycobacterium TB infection and disease in adult patients with CKD. Thorax 2010; 65: 559-570

4900 Prednisolone treatment does affect the performance of the Quantiferon in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis

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Background: During screening for latent tuberculosis infection (LTBI), before anti-TNF-alpha treatment, most patients are already receiving immunosuppressive therapy. Objectives was to evaluate the performance of the Quantiferon IN-Tube (QFT-IT) and the Tuberculin Skin Test (TST) in these groups.

Methods: We included 244 patients treated for ulcerative Colitis, Crohn’s disease, rheumatoid arthritis, and spondylo-arthropathy. Results: QFT-IT was positive in 72/48 (3%), negative in 299 (92%), and indeterminate in 2/5 (4%). TST was positive in 54/238 (23%) patients. Chest X-ray was suspect in 53/256 (21%), and 35/167 (21%) had risk factors. We found a pronounced negative effect on QFT-IT and TST performance associated with prednisolone treatment; the IN- response to mitogen stimulation was impaired (median INP- response 4.91/ml (IQR 0.8-10.0) compared to patients a) not receiving corticosteroids (median 10.0 (IQR 5.0-10.0) (p=0.0015) or b) receiving long-acting corticosteroids (median 10.0 (IQR 9.7-10.0) (p=0.0058). Prednisolone treatment was strongly associated with negative TST, AOR 22 (0.1-0.8) (p=0.018), and with an increased risk of indeterminate QFT-IT results AOR (16.1-9.0) (p=0.001). No negative effect was found for long-acting corticosteroids. Prednisolone doses above 10mg resulted in 27% of indeterminate results.

Conclusion: Oral prednisolone severely suppressed QFT-IT and TST performance whereas long-acting corticosteroids, Metotrexate, Azathioprin and 5-ASA did not have similar detrimental effect. Patients should be screened for LTBI with QFT-IT or TST prior to initiation of prednisolone.

508. Novel mechanisms in COPD

4901 Results of a phase 2a clinical trial with a peptide inhibitor of MARCKS protein indicate improvement of indices of bronchitis and lung function in patients with COPD

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A peptide inhibitor of MARCKS (BIO-11006) attenuates mucus hypersecretion, inflammatory cell influx and airway obstruction in several in vivo models of asthma and bronchitis, suggesting BIO-11006 as an ideal treatment for COPD. In a Phase 2a study, 172 subjects with stable COPD (GOLD Stage 2, 3) were randomized in a double blind, controlled safety and efficacy study. Four doses of BIO-11006 or control (half normal saline; HNS) were administered by nebulization for 21 days to 5 cohorts; 75 mg QD (n=8) or BID (n=24), 150 mg QD (n=35), and 25 mg BID (n=32); HNS (n=40). The ratio of active control was 2:1 and 3:1 for QD and BID dosing, respectively. Trough FEV1 (primary endpoint) was measured on days 0, 3, 7, 14, 21, 28 and 49. A trend towards increased FEV1 with the 75mg BID group was maintained on follow-up days 28 and 49. An FEVI responder analysis (defined as 5% or more improvement of FEV1 = Responder) revealed the percentages of responders for the 75 mg BID dose were 46, 38, 50 (p=0.014 vs HNS), 42, 54 (p=0.014 vs BID 150mg) and 40% vs 150mg, respectively. BIO-11006 was systemically well tolerated with some increase in respiratory adverse events. We conclude that the 75 mg BID dose appeared to be the most efficacious by increasing the proportion of FEV1 responders statistically significantly as compared with HNS. Sputum volume and the St Georges Respiratory Questionnaire Symptoms Score also trended towards improvement with 75mg BID. Thus, BIO-11006, a dual action molecule that decreases both mucus hypersecretion and inflammation, may represent a new advance in the treatment of COPD.

4902 Discrimination of expanded dendritic cell populations in lung tissues from COPD patients

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Rationale: Dendritic cells (DCs) are highly plastic and their characterization in human tissues has been hampered by lack of standardized immunohistochemical identification. This study validates an immunohistochemical approach for discriminating confounding non-DC cells and characterizes multiple DC populations in COPD-affected lungs.

Methods: Lung specimens were obtained from 27 COPD patients and divided into three tissue levels of severity: GOLD I (n=6), GOLD II-III (n=11) and GOLD IV (n=10). Never-smokers (n=8) and non-COPD smokers (n=6) served as controls. Paraflin sections were double stained for combinations of macrophage and DC markers.

Results: Using the non-soluble DAB as the first detection chromogen it was possible to mask confounding non-DC cells e.g. CD68 macrophages at a bright microscopic level. Using this approach two populations of CD68+CD11c+ and CD68-CD11c+ cells were identified, and their immunophenotyping is described. The myeloid DCs, which were foremost BDCA3+, significantly increased in diseased areas of COPD lungs, in particular in patchy areas of fibrosis and granuloma formation. Both CD68+CD11c+ and CD68-CD11c+ cells displayed a dendritic morphology and were located in epithelial and subepithelial compartments of small airways and alveolar walls as well as in lymphoid aggregates amidst CD21+ follicular DCs. Further combination of markers could discriminate intrapulmonary myeloid and plasmacytoid DCs from CD207+ and CD11c+ epithelial DCs.

Conclusions: This study demonstrates that masking of confounding non-DC pop-ulations improves the identification of lung DC populations and reveals novel aspects of their dynamics and heterogeneity in COPD lungs.

4903 Mechanisms of tertiary lymphoid organ formation during lung neogenesis are involved in lymphoid follicle formation in chronic obstructive pulmonary disease

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Tertiary lymphoid organs (TLOs) are aggregates of B and T cells formed in response to chronic immune responses. TLOs are the result of lymphoid neogenesis and are formed via production of lymphoid-organizing chemokines (CXCL13, CCL19 and CCL21), in response to signaling from lymphotactin (LTα) via TNFR1, TNFR2 and LTR. Stromal cells and antigen presenting cells (APCs), i.e. dendritic cells (DCs), secrete lymphoid chemokines, which attract B cells, T cells and DCs via CCR7 (receptor for CCL19/21) and CXCR5 (receptor for CXCL13). Lymphoid follicles are frequently found in the peripheral lungs of patients with Chronic Obstructive Pulmonary Disease (COPD). Whether they are the result of lymphoid neogenesis remains elusive. Here, we have identified 18 patients with COPD and lymphoid follicles and used immunohistochemistry to analyze the expression of LTα and lymphoid chemokines. Flow cytometry was applied to study expression of LTα and CD21+ follicular DCs, expressed by alveolar macrophages and lung stromal cells and CXCL13 is strongly expressed inside the follicles. HLA-DR+ve cells (APCs), but not CD45-ve stromal cells, strongly express TNFR2 (43% of APCs), TNFR2 (47%) and LTR (38%). CXCR5 is expressed by B cells (96% of B cells), DCs (74% of DCs) and T cells (24% of T cells). CCL19, CCL21 and CCR7 are rarely expressed. In conclusion, molecular mechanisms underlying TLO formation might be involved in lymphoid follicle formation in COPD as follows: stromal cells and macrophages secrete LTα, which induces CXCL13 production by lung APCs, driving the accumulation of CXCR5+
Cigarette smoke-induced oxidative modification of creatinine kinase B (CKB) is involved in the pathogenesis of COPD in terms of acceleration of bronchial epithelial senescence.

**Introduction:** Cigarette smoke accelerates cell senescence, implicated in COPD pathogenesis. Energy status is one of the most crucial determinants for aging and longevity. In cells, current energy metabolism, oxidative stress, and various pro-inflammatory mediators contribute to cell senescence. To characterize autophagic degradation of cell organelles, we hypothesized that CKB might also be oxidized and lost activities by smoking stress, resulting in disease pathogenesis of COPD in terms of acceleration of cell senescence.

**Aims:** To elucidate the role of CKB in cigarette smoke extract (CSE)-induced cellular senescence in human bronchial epithelial cells (HBEC).

**Methods:** Primary HBEC and BEas2B cells were used. Senescence was evaluated by SA-β-gal staining and p21 expression and cell cycle analysis. CKB was inhibited by sRNA and cycloheximide. Interleukin (IL)-8 secretion were measured by ELISA.

**Results:** CSE induced carboxylation of CKB and decreased CKB protein levels, and this decrease was reversed by the proteasome inhibitor. CSE induced cell senescence, and CKB inhibition further enhanced CSE-induced cell senescence. CSE treatment caused increased amounts of IL-8 secretion, a hallmark of senescent associated secretory phenotype (SASP). IL-8 secretion was further increased by CKB ablation.

**Conclusions:** CSE induces carboxylation and subsequent proteasomal degradation of CKB, and decrease of CKB is implicated in the regulation of cell senescence with SASP.

**4906**

Up-regulation of decoy receptor D6 in COPD

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**Introduction:** Insufficient autophagy is involved in accelerated cellular senescence in the pathophysiology of COPD.

**Aims:** To elucidate the role of autophagy in cigarette smoke extract (CSE)-induced cellular senescence in human bronchial epithelial cells (HBEC).

**Methods:** HBEC was isolated from lobectomy specimens. To characterize autophagic degradation of cell organelles, we hypothesized that CKB might also be oxidized and lost activities by smoking stress, resulting in disease pathogenesis of COPD in terms of acceleration of cell senescence.

**Conclusion:** These findings implicate airspace SAA signaling as a mediator of GC-resistant systemic COPD biomarker and hence, characterized its function in orchestrating mucosal inflammatory responses that contribute to neutrophil accumulation.

**4907**

Serum amyloid A augments mucosal immunity by opposing resolving lipoxin A4 signaling in chronic lung disease.

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**Introduction:** Persistent innate immune activation contributes to tissue destruction in chronic obstructive pulmonary disease (COPD). A histone demethylase inhibitor, 3-deazaneplanocin A (D6), suppresses inflammation in COPD. We previously identified SAA as a GC resistant systemic COPD biomarker and here, characterized its function in orchestrating mucosal inflammatory responses that contribute to neutrophil accumulation.

Methods: Three separate patient cohorts were investigated involving 81 patients. Results: In a prospective study of competing ALX/P2RX2 ligands during COPD exacerbation, circulating SAA levels were markedly and disproportionately increased relative to LXA4. Secreted SAA levels in COPD BAL fluid correlated with interleukin-8 and the neutrophil activation marker, neutrophil elastase. SAA was also detected in COPD lung in close proximity to airway epithelia, and in vitro SAA triggered pro-inflammatory mediator (MCP-1, GM-CSF and IL-8) release by airway epithelial cells in an ALX/P2RX2 receptor-dependent manner. Lipoxin A4 (LXA4) blocked SAA initial epithelial responses via allosteric inhibition. Exhalation LXA4 (pA2 13.3 pm) inhibited smoking-induced acute inflammation that was significantly inhibited by equivalent amounts of 5-epi-LXA4 but not dexamethasone. Tissue macrophages (CD68+), polarised with lung SAA and the GC-dexamethasone markedly increased SAA production by THP-1 macrophages (pEC50 43.4 pm).

**Conclusions:** Together, these findings implicate airspace SAA production as a mediator of GC resistant lung inflammation that can overwhelm organ protective signaling by lipoxins at ALX/P2RX2 receptors.
ing and western blotting of p21 were performed to evaluate cellular senescence. Interleukin (IL)-8 was measured by ELISA.

Results: CSE-induced cellular senescence was accompanied by accumulations of ubiquitinated proteins and p21. Although CSE transiently induced autophagy, it was insufficient to inhibit cellular senescence. Increased autophagy suppressed CSE-induced senescence and accumulations of these proteins. In contrast, inhibition of autophagy enhanced not only senescence but also the senescence-associated secretory phenotype (SASP) of IL-8 expression.

Conclusions: These results suggest a potential regulatory role for autophagy in CSE-induced cellular senescence with SASP by preventing the accumulation of ubiquitinated proteins and p21.

509. Clinical features of human pulmonary hypertension

4099 Late-breaking abstract: Demographic trends and changes in long term outcome of incident idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension between 2001 to 2009. Results from the Pulmonary Hypertension Registry of the United Kingdom and Ireland

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Background: There have been significant changes in the management of pulmonary arterial hypertension (PAH) over the past decade. In the UK and Ireland, care of pulmonary hypertension (PH) is centralised to designated PH centres. This provides an excellent opportunity to study changes in demographic and survival trends of the disease within an entire region with a common healthcare system.

Aim: To determine whether baseline characteristics and survival of incident iPAH, heritable and anorexigen-associated PAH has changed over the past decade.

Methods: Retrospective observational study of all incident cases of iPAH, heritable and anorexigen-associated PAH diagnosed in the UK and Ireland between 1st January 2001 and 31st December 2009.

Results: Total of 646 patients were diagnosed (22% in 2001-2003, 33% in 2004-2006 and 45% in 2007-2009). In recent years, patients were older, had higher BMI, lower % predicted diffusion capacity for carbon monoxide (%DLCO) and exercise capacity (6 minute walk distance). BMI, lower % predicted diffusion capacity for carbon monoxide (DLCO) and exercise capacity (6 minute walk distance and cardiac index, patients with mean PAP >25 mmHg at RHC were considered to have PHLHD. It can be difficult to distinguish pulmonary arterial hypertension (PAH) from left heart disease (PHLHD). Current practice is to use right heart catheterisation (RHC) which will respond to disease targeted therapy) from pulmonary hypertension due to heart failure. These results suggest a potential regulatory role for autophagy in CSE-induced cellular senescence with SASP by preventing the accumulation of ubiquitinated proteins and p21.

Conclusion: In PAH it is possible to identify a subgroup of patients with PAH hypotropenia and moderate diastolic volume increase (i.e. high RV mass/volume ratio) which has a low rate of deaths, suggesting a better RV adaptation to the increased afterload.

4911 Pulmonary arterial hypertension in patients with chronic kidney disease on dialysis and without dialysis

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Background: Pulmonary hypertension (PH) is common in patients with dialysis-dependent chronic kidney disease (CKD) due to an increased prevalence of PH. However, specific hemodynamics of the pulmonary circulation, changes induced by hemodialysis and prevalence of pulmonary arterial hypertension (PAH) have not been evaluated in patients with CKD.

Methods and results: We assessed consecutive patients with CKD on hemodialysis (group 1, n=31) or without dialysis (group 2, n=31), in World Health Organization functional class >II with dyspnea unexplained by other causes, using right heart catheterization (RHC). In group 1 RHC was performed before and after dialysis. PAH was diagnosed if mean pulmonary arterial pressure (mPAP) was >25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg (after dialysis in group 1) and if other causes of PH were excluded. In CKD patients after dialysis, prevalence of PH was 24/31 (77%; 20/31 postcapillary PH, 4/31 precapillary PH); prevalence of PAH was 3/31 (10%). After dialysis, there were significant decreases in mPAP and PCWP; all four cases of precapillary PH were unmasked by dialysis. Patients in group 2, postcapillary PH was diagnosed in 22 cases (71%); no cases of PAH were detected.

Conclusions: The finding that the prevalence of PAH was 10% in CKD patients on dialysis and without dialysis unexplained dyspnea suggests careful screening for PH in this patient population is warranted. The possibility that dialysis might be a trigger for the development of PH is plausible given that there were no instances of PAH in the nondialysis CKD patient group. RCH should be performed after dialysis to unmask precapillary PH.

4912 Left atrial volume to distinguish idiopathic pulmonary arterial hypertension from pulmonary hypertension due to left heart disease

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Introduction: It can be difficult to distinguish pulmonary arterial hypertension (which will respond to disease targeted therapy) from pulmonary hypertension due to left heart disease (PHLHD). Current practice is to use right heart catheterisation (RHC) to distinguish between the two conditions. We explored the use of left atrial volume (LAV) obtained via cardiac magnetic resonance imaging (CMR) as an alternative to RHC.

Methods: Patients being admitted for diagnostic assessment underwent CMR and RCH. LA volume was assessed using standard 2- and 4-chamber CMR views and the biplane area-length method, and indexed to the body surface area. RHC was then performed within 72 hours. PAH was defined as per current guidelines. Patients in group 2, postcapillary PH was diagnosed in 22 cases (71%); no cases of PAH were detected.

Results: Between Jan 2009 and Feb 2011 we diagnosed 31 patients with PAH (mPAP 47±10, PCWP 7±4 mmHg) and 19 patients with PHLHD (mPAP 43±8, PCWP 22±6 mmHg). LAV was significantly lower in PAH compared with PHLHD (24±9 ml/m² vs 66±19 ml/m², p<0.0001). Using an LAV threshold of 43 ml/m²
High altitude pulmonary edema (HAPE) is a non-cardiogenic pulmonary edema that develops in susceptible people at high altitudes. The pathogenesis remains to be conclusively elucidated and genetic polymorphisms were highly proposed to be associated with HAPE. The aim of this study is to identify the locations of the candidate human genes those might associate with the HAPE susceptibility or resistance.

**Methods:** We performed a genomewide association study in 53 Japanese patients with high-altitude pulmonary edema (HAPE) who had developed HAPE during climbing mountains higher than 2500 m and the control group enrolled 67 Japanese resistant subjects (HAPE-r). The control group included patients without a family history of HAPE. A case-control association study was performed using 400 polymorphic microsatellite markers (which define about 10 centiMorgan resolution throughout the whole genome) by PCR. The PCR-amplified products were sequenced automatically by Gene Scan software.

**Results:** Nine markers (D1S468, D1S2697, D1S2785, D4S405, D5S424, D6S257, D1S2638, D16S3103 and D21S120) showed statistically significant associations with the susceptibility to HAPE and three markers (D1S230, D14S283 and D22S280) showed significant associations with the resistance to HAPE. These markers were in linkage with genes controlling pulmonary alveolar structure, chloride channel, endocrine proteins, and other factors those might play important roles in the development of HAPE.

**Conclusion:** This is the first genomewide association study in HAPE. It revealed several candidate genes in associations with HAPE. The development of HAPE may be determined by the interaction of multiple genes.
510. Asthma: improving diagnosis and management for reaching better control

P4917 Including variability as a criteria, increases diagnostic accuracy in elite asthmatic swimmers after mannitol and exercise challenge
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Increased frequency of asthma has been reported among swimmers, but many tests have a low sensitivity to detect asthma among elite athletes. The aim was to investigate the prevalence of asthma among elite swimmers, to compare sport specific exercise test with Mannitol and explore the tests ability to detect asthma.

Methods: 101 elite swimmers (14-24 years) performed both Mannitol provocation and a sport specific exercise test. Mannitol positivity was defined as either direct FEV1, PD15 or as f2: reversibility ≥ 15% after challenge (extended criteria). A direct positive exercise test was defined as a drop in FEV1 of 10% compared to baseline or a difference in FEV1 of <15% either spontaneous, variability or with β2-agonist, reversibility (extended criteria).

Results: We found a high prevalence of Mannitol and/or Exercise positivity. For Mannitol, 26 were positive by ordinary criteria and 43 with extended criteria. The corresponding numbers for exercise test were 14 and 24. When including reversibility and variability to define a positive test the sensitivity to detect current asthma with or without exercise induced symptoms increased while the specificity remained unchanged. Direct positivity for Mannitol or Exercise poorly overlapped using ordinary criteria.

Conclusion: We found a high prevalence of EIA among elite swimmers. The use of variability and reversibility as additional criteria to define a positive test increased the ability to detect asthma with or without exercise induced symptoms, without lowering the specificity, and should therefore be considered in the interpretation of the tests.

P4918 Asthma severity and duration influence to fetoplacental circulation
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Hemodynamic of fetoplacental circulation in Asthmatic patients is not studied enough yet. Modern data on asthma severity duration and its control influence to fetoplacental circulation are still lack and controversial. The goal of our study was investigation of fetoplacental circulation with ultrasonic dopplerography. Pregnants with different asthma severity and treatment were studied at 34 week of gestation.

Materials & methods: 73 Asthmatic pregnant were studied (5 - severe persistent, 18 - moderate persistent, 22 - mild persistent & 28 - mild intermittent). 64 females without lung pathology were studied also as a control group (K). ICS were administered to 55 patients. Among them 17 rejected ICS use and were administered SABA with other medications instead. Systolo-diastolic ratio (SD) in uterine (UA), umbilical (UmA) and fetus medial cerebral (ACM) arteries was measured.

Results: SD was increased in UA and ACM within asthmatics, but with no significantly differences. In moderate persistent asthma SD was significantly higher in UA (2.51±0.29) in comparison with mild persistent (1.91±0.18) and with K (1.59±0.13) (p<0.05). In pregnant, who undergone asthma relapse during the first trimester SD in UA (2.69±0.12) differed (p<0.05) in comparison with K. Reliable UA and ACM SD level differences were accepted in patients with moderate persistent asthma, who were administered ICS to ICS free patients (1.91±0.15 to 2.82±0.59) and (4.39±0.43 to 5.98±0.68) respectively (p<0.05).

Conclusion: Relapse of Asthma in the first trimester of pregnancy, severity of Asthma and absence of basic therapy influence level of the blood flow in UA. Absence of basic therapy leads to increase of blood pressure in ACM of fetus.

P4919 Genetic characterization of the association between asthma and obesity.
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Introduction: The inflammatory way of the TNF-alfa could be a mutual way of the asthma-obesity phenotype.

Objective: To evaluate if the presence of polymorphisms at the promoter of gene TNF-alfa-308 G/A is related with an asthma-obesity phenotype and determines the severity of the disease measured by the number of exacerbations.

Methods: We included blood samples of 48 asthmatics. To determine the presence of polymorphism -308G/A in the promoter region of TNF-alpha gene, we performed the technique of chain reaction (PCR) followed by the generation of restriction fragments and digestion of the amplified product. The product of digestion was visualized in a gel of 3% agarose. This allowed us to distinguish native allele TNF-1 with 2 fragments of restriction, 87bp and 20 bp and polymorphic allele TNF-2 of 107 bp.

Results: The average age 28±4.6 years, 83% men. Genotype distribution was: AA (4%), AG (23%) and GG (73%). No statistically significant differences were found between different alleles and IMC. When we analyzed the evolution of disease considering the number of exacerbations we observed that presence of allele A determines greater number of exacerbations during the year (p=0.02).

Conclusions: The presence of the allele A has been associated with a worse prognosis as measured by the number of exacerbations, which could be explained by an increase in promoter activity and TNF secretion.

P4920 Prevalence depression – Anxiety and impact on quality of life, asthma control and asthma severity in adult patients with asthma
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We examined the prevalence of depression and anxiety, and impact of depression...
and anxiety on quality of life, and treatment response of disease in patients with asthma.

Demographic data, smoking, allergy, atopy, additional diseases, age at asthma, age diagnosis <25 year, and body mass index was (BMI) calculated. Hospital Anxiety Depression Scale (HADS), Asthma Quality of Life Questionnaires (AQLQ) in the subjects were evaluated.

The sample consisted of 414 subjects (73% female) with a mean age of 47.6±13.8 years. Regarding chronic severity, 9.8% were intermittent, 63.2% mild persistent, 24.4% moderate persistent, and 2.6% severe persistent. Furthermore, 44.1% of the patients were controlled, 47.9% were partly controlled/controlled/fine were uncontrolled. Rates of physician-diagnosed depression and anxiety were 10.4% and 2.9%. Regarding HADS, anxiety score was ≥10 in 37.4% and depression score ≥7 in 50.2% of the subjects. Prevalence of physician-diagnosed depression was significantly higher in women (p<0.05). Regarding AQLQ results, there were negative correlations between scores of symptoms, activity limitations, emotional function, environmental stimuli and severity. AQLQ scores were lower in subjects with physician diagnosed depression (p=0.000). There were negative correlations between AQLQ scores and HADS depression-anxiety scores (p=0.000).

It is suggested that depression and anxiety are associated with worse asthma control and quality of life. Physicians should consider depression and anxiety in patients with worse controlled asthma and quality of life in spite of optimal therapy for asthma.

**P4923**

**Asthma and metabolic syndrome**

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**Background:** The study aims to analyze the psychometric properties of Portuguese version of scale Ways of Coping with Asthma in Everyday Life – WCAEL (Aalto et al, 2002), developed to measure coping in everyday life in asthmatics.

**Methods:** Cross-sectional study with 253 patients, both sexes, with asthma diagnosed, recruited consecutively from the Allergy & Asthma outpatient clinic (HS João/Porto). Exclusion criterion were: psychiatric disease and alcohol/drugs abuse. A total of 247 patients were evaluated with the following scales (Portuguese versions): Ways of Coping with Asthma in Everyday Life - WCAEL, Problem Solving Inventory – PSI and Asthma Control Questionnaire – ACQ. A subsample of patients (n=50) was followed for four weeks. These patients also were classified according severity of asthma (GINA, 2006) and the duration of the illness.

**Results:** The participants were mostly females (78.5%), with a mean (sd) age of 40.6±(15.3) years. The majority (78.7%) had severe persistent asthma and the mean duration of the illness was 20.8±(15.4) years. In the final factor analysis of principal component method (varimax rotation) 4 factors were extracted (explaining 46.3% of total variance). The internal consistency values were moderate (α=0.56-0.67). WCAEL showed significant associations with ACQ, as well as good reproducibility over time (r=0.58-0.76).

**Conclusion:** The study data support the reliability, construct and criterion validity of the Portuguese version of WCAEL seems a promising scale for assessment the coping with asthma in everyday life.

**P4924**

**Elderly patients associated with poor asthma control and quality of life in Spanish asthmatics**

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**Background:** Several risk factors determined asthma control, which is a fundamental objective in patients’ management, however it is still insufficient.

**Objective:** To assess how the lack of asthma control affects quality of life and which are the main factors associated.

**Methods:** Observational, cross-sectional and multicenter study that included severe asthmatic patients. We assessed quality of life (QoL) using Mini-AQLQ questionnaires, anxiety and depression using Hospital Anxiety and Depression Scale, and hyperventilation by Nijmegen questionnaire.

**Results:** 343 patients participated in the study, 67.6% women. Mean age (SD) of asthma uncontrolled patients was slightly higher, especially when analyzed according to Spanish Guidelines for Asthma Management (GEMA) [48.5±(14.7) vs 44.1 (14.1) years, p<0.079]. A higher BMI was observed in uncontrolled patients [28.2 (5.8) kg/m² vs 25.5 (4.9) kg/m², p=0.006]. Smoking habit was not related to asthma control.

**Conclusions:** Uncontrolled asthma showed a worse quality of life, showing higher levels of anxiety, depression and hyperventilation.
Severely obese (BMI) ≥ 35, n=119 women with and without physician-asthma diagnosis at any time (32 [27%], 11 diagnosed in childhood), healthy women (37, 30 without AHR, with BMI <25) underwent pulmonary function testing (tidal ventilation monitoring, spirometry, plethysmography, fractional exhaled NO, metabolite challenge) and overnight ambulatory polynography. No, possible (compatible symptoms, whatever the presence of AHR), probable (AHR, suggestive symptoms, Asthma Control Questionnaire ≥ 0.75) and confirmed asthma (AHR, suggestive symptoms, Questionnaire > 0.75) were established in obese women. An additional group of asthmatic women (BMI < 25, n=14) underwent pulmonary function tests to allow control with confirmed obese asthmatic patients.

P4927
Are there lower blood CO2-levels in asthmatic patients? Sarah Ernst, Jörg D. Leuppi, Prashant N. Chhajed, David Miedinger. Respiratory and Internal Medicine, University Hospital Basel, Basel, Switzerland.

Background: Dysfunctional breathing was shown to be common in people with asthma and therefore breathing retraining might be an additional therapy beside asthma medication. However it is unclear if dysfunctional breathing is associated with lower blood CO2-levels in asthma patients compared to healthy subjects.

Objectives: To find out if there is any relevant difference in blood CO2-levels comparing subjects with and without asthma.

Methods: 138 currently employed municipal firefighters and policemen from Basel, Switzerland underwent methacholine bronchoprovocation testing (MCH) according to a standardized protocol. We assigned a diagnosis of asthma according to three widely used definitions: Having 1) a positive MCH test (MCH+), 2) physician-diagnosed asthma and 3) wheezing in the last twelve months and a positive MCH test (Wheeze/MCH+). We compared transcutaneously measured blood CO2-levels (TcCO2-levels) of subjects with and without asthma at rest prior (PRE), one and five minutes after (MIN, 5MIN) MCH challenge.

Results: At rest and at 5MIN, no significant differences were measured between asthmatic and non-asthmatic individuals for all three definitions. At 1 MIN, asthmatics had higher TcCO2-levels than non-asthmatics only if using the MCH+ definition (TcCO2 vs 33.4 ± 6.0 mmHg, p = 0.023; physician diagnosed asthma: 35.8 vs 33.6 mmHg, p = 0.072; Wheeze/MCH+: 36.3 vs 33.6 mmHg, p = 0.052).

Conclusions: Resting TcCO2-levels were not different in our sample of individuals with or without asthma according to diverse disease definitions and thus do not support the presence of relevant dysfunctional breathing at rest. At one minute after provocation challenge, metacoline positive subjects had higher TcCO2-levels than the negative ones.

P4928
Effect of BMI on asthma control, asthma severity and quality of life in adult patients with asthma Aysegul Altintop, Haydar Karakus, Zeynep Aytemur, Sukelyan Haciveyliyagil, Hilal Erdem. Department of Pulmonary Disease, Ege University School of Medicine, Izmir, Turkey.

We examined effects of body mass index (BMI) on quality of life, asthma severity and treatment response of disease in patients with asthma. Demographic data, occupation and education status, symptoms, smoking, allergy, atopy, additional diseases, age started asthma, age diagnosed asthma, and drugs of subjects were recorded, and body mass index was calculated. Hospital-Anxiety Depression Scale (HADS), Asthma Quality of Life Questionnaires (AQLQ) in the subjects were evaluated.

The sample consisted of 414 subjects (73% female) with a mean age of 47.6±13.8 years. Regarding chronic severity, 9.8% were intermittent, 63.2% mild persistent, 24.4% moderate persistent, and 2.6% severe persistent. Furthermore, 44.1% of the subjects were controlled asthma, 47.9% partly controlled, 8% uncontrolled.

Patients were considered to be obese if their BMI was ≥ 30 kg/m². BMI was mean 26.6±5.37 kg/m² in men and 28.8±6.21 kg/m² in women (p<0.05). There was no correlation between BMI and severity of asthma control. There was a positive correlation between BMI and age started asthma (p=0.05). Regarding AQLQ results, there were negative correlations between scores of symptoms, activity limitations, emotional function, environmental stimuli and severity asthma (p<0.05). There were negative correlations between only environmental stimuli, activity limitations and BMI (p<0.05). There was no correlations between BMI and HADS depression-anxiety scores, physician-diagnosed depression-anxiety.

Our findings suggest that obesity is associated with poor asthma-specific quality of life. BMI control was important as well as optimal asthma therapy in patients with asthma for optimal asthma control.

P4929
Controlled asthma in atopic and non atopic patients: Is needed a different approach? Angelo Petrosianni, Vittoria Conti, Valentina Giunta, Michela Lagallà, Marcella Lilli, Ambra Castagnaci, Augusto Bevilacqua, Safia Khan Kaïl, Claudio Terzano. Department of Cardiovascular and Respiratory Sciences, Sapientia University of Rome, Rome, Italy.

Background: Allergy is a significant trigger for asthmatic exacerbation. Currently, the control of asthma is mainly based on the absence of symptoms and airway obstruction.

Aim: To evaluate the difference in atopic (AT) and non atopic (N-AT) patients with controlled asthma on the risk of exacerbation and step up therapy.

Methods: 98 asthmatic pts with ACT (Asthma Control Test) > 20 were enrolled in a 3yrs randomized controlled trial. Pts were divided in 2 groups: Group A (ICS) receiving a continuous treatment with inhaled beclometasone MDI100mcg twice/day +inhaled saltubrate as needed; Group B (control) treated with inhaled saltubrate as needed. Step up therapy was performed as recommended by guidelines. Pct tests for the most common allergens were performed at the enrolment.

Aim: Endpoint were exacerbations, 3mths ACTCore, and drug as needed.

Results: 80 pts (A93, B41) concluded the study; asthmatic pts were in A 29 (74%), in B 27 (66%). In Group A no significant difference was reported for exacerbations (AT4.2, N-AT3.9) and ACT (AT3.19, N-AT2.4), whereas in Group B slight significant differences reported for exacerbations (AT4.8*, N-AT3.9) and ACT (AT18.6*, N-AT20.1).

Interestingly, analyzing data in multisensitized ≥ 3 classes of allergens) and low-sensitized (< 3 classes of allergens) AT pts, a significant difference (*) was reported in both groups: exacerbations in A (multis. (16pts) 4.8*, N-AT3.9), in B (multis. (15pts) 5.6*, N-AT3.98); ACT in A (multis. 19.1, N-AT20.4), in B (multis. 17.5*, N-AT20.1).

Conclusion: Pts with controlled asthma and atopy show a protective effect on exacerbations during a long term treatment with low dosage ICS. Moreover, multisensitized pts with controlled asthma report an high risk of exacerbation than non atopic.

P4930
Asthma at treated patients correlations between treatment, level of control and exacerbations in a pneumology department Diana Dimitri1, Carmen Ardelean2, Stefan Frent3, Voicu Tudorache2,3, Ioan Marinici2, Stefan Mihaiacuta2. 1Pneumology, St. Maria Medical Center, Timisoara, Romania; 2Pneumology, Victor Babes Hospital of Infectious Diseases and Pneumology, Timisoara, Romania; 3Pneumology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania.

Introduction: Uncontrolled bronchial asthma (BA) is a serious problem, altering the quality of life, and consuming a lot of resources. Aim: Evaluation of the factors related to lack of control.

Material and method: Between October 2007 and Mars 2009 we evaluated 584 consecutive patients at V.Babes Hospital, Timisoara, Romania, known and treated for BA, and collected general data, medical history, disease onset, spirometry, treatment duration, treatment, asthma control test (ACT), level of control GINA 2007. The association of variables was analyzed by calculating the odds ratio (OR) together with confidence intervals (CI) in a univariate analysis. The significant independent variables were utilized to create models of multivariate logistic analysis in order to identify the most important predictors.

Results: 584 patients, 162 males (27.74%), 422 females (72.26%), mean age 45.37 years (14-85), 24 smokers, ACT <18 (36.2%), 20-24 (48.8%), 25 (15.5%), 31.3% exacerbations, 78.46% patients with inhaled corticosteroids (ICS) in combination or in monotherapy, 63.4% with normal spirometry, 52.5% with allergy, 11.3% occupational exposure, 4 predictors for uncontrolled BA: exacerbations OR 4.11, CI 3.30-7.48, p <.001, occupational exposure OR 2.29, CI 1.23-4.26, p =0.009, altered lung function on spirometry OR =1.18, CI 1.02-1.36, p=0.021 (obstruction OR 3.78 CI 1.76-7.78, p <0.001), duration of disease (months) OR=1.02, CI 1.00-1.03, p=0.021.

Conclusions: Despite treatment with ICS, more than 1/3 (36, 2%) of patients had uncontrolled asthma. Exacerbation and occupational exposure are the most powerful predictors.

P4931
Phenotypic differences between atopic and non atopic patients with asthma Takahiro Yoshikawa1, Hiroshi Kanazawa 2, Kazuto Hirata 2.

1Sports Medicine, Osaka University City Graduate School of Medicine, Osaka, Japan; 2Respiratory Medicine, Osaka University City Graduate School of Medicine, Osaka, Japan.

Background: The present study aimed to illustrate differences in characteristics and perception of dyspnea between young atopic adults who have no history of asthma (never-asthmatics) with or without asymptomatic airway hyperresponsiveness (AHR) and those who had childhood asthma and consider themselves to be grown out of the disease (past-asthmatics).

Methods: Blood parameters, lung function and methacholine PC20 were measured in never-asthmatics and 24 past-asthmatics. A perception score of dyspnea at 20% fall in FEV1 (FEV1s) was obtained by interpolation of the two last points on the perception (modified Borg scale) fall in FEV1 curve during methacholine challenge.

899s
Results: Thirty-one of 88 never-asthmatics and eighteen of 24 past-asthmatics exhibited AHR (PC_{20} was ~8 mg/ml). Higher levels of specific IgE to house dust mite in past-asthmatics were observed than never-asthmatics with and without AHR. Mean values of FEV1 and FEF_{25-75} (predicted) were significantly lower in past-asthmatics than never-asthmatics without AHR, and the values in never-asthmatics with AHR were intermediate between never-asthmatics without AHR and past-asthmatics. PC_{20} were not significantly different between past-asthmatics and never-asthmatics with AHR. Of particular interest was that PS_{24} was significantly lower in never-asthmatics with AHR compared with past-asthmatics.

Conclusions: The present findings suggest the possibilities that presence of absence of past history of outgrowth of childhood asthma might be associated with airway narrowing, sensitization to house-dust mite and perception of dyspepsia in young asymptomatic adults with atopy and AHR.

P4932 Evaluation of asthma knowledge and quality of life in adult patients with asthma
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Asthma is a chronic illness that affects the everyday life of patients who suffer from it and is a cause of quality of life impairment in adults. Patients with asthma were studied in order to establish the level of knowledge concerning asthma and the degree quality of life impairment due to asthma. The purpose is to evaluate the quantitative relationships between the level of knowledge and quality of life in adult Asthmatics. Through 2010 year, 242 subjects were recruited from the Allergy Outpatients. Patients from 18 year of age to 51 year old were eligible. Patients completed the asthma knowledge questionnaire and asthma-related quality of life questionnaire (SGRQ) at second physician visit, after the educational information. The level of Knowledge Asthma was measured using the questionnaire of the asthma knowledge. Response options were presented as true/false. Each question had a score of one (maximum score of 24). Mean asthma knowledge score in the population was equal to 11.71. Overall scores ranged from 25% to 75%. The asthma knowledge score was correlated significantly with the symptoms domain (R=0.45, p <0.001), the activity domain (R=0.20, p=0.002), the impact domain (R=0.29, p <0.001) and the SGRQ total score (R=0.29, p <0.001). A negative value of Spearman’s rank correlation coefficient means that the patients who obtained high scores in the asthma knowledge questionnaire had a tendency to have a low score in the SGRQ (at second physician visit). This study shows that level of knowledge asthma correlate with domains of asthma-related quality of life by SGRQ. The results suggest that is it necessary to asthmatic knowledge to achieve long-term effectiveness of asthma control and QoL.

P4933 Adult-onset asthma: Risk factors
Teresa Gomez Garcia1, Javier De Miguel Diez1, Roberto Pelta Fernandez1, M Carmen Juez Morales1, Lihana Moran Caicedo1, Veronica Sanz de Burgos1, Julia Gil-Magran1, Ana Pégorié1, Nicolas Paleiron1, Thomas Erasco1, Cecile Troumèr1, Sophie Herry1, Yvan Bec2, Bertrand Bouard3, Frédéric Grassin3, Michel Andéol1
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To determine the risk factors for the development of asthma in patients older than 12 years.

Methods: An observational, transversal, multicentric, case-control study was led from May to October 2009 in Spain. Patients over 12 years old, diagnosed of asthma in the last 12 months that went to a pneumologist or allergist clinic for any reason were chosen as cases. Each case had at least a non-asthmatic control chosen as cases. Each case had at least a non-asthmatic control chosen. Among 391 workers 353 (90%) participated in the study, 52 of whom (15%) had a high risk (sumscore ≥ 5) and were candidate for medical evaluation, including a low-dose high resolution CT-scan of the lungs.

Results: Of 48 of 52 workers (response 92%) were referred for clinical evaluation. Mean age was 52 (±5) yrs, number of pack years 28 (±21). Silicosis was found in 8 workers (17%), another 3 in a new number of micromodules on CT (6%). In addition, COPD was present in 6 workers (13%): Gold I in 2 (one of whom had silicosis), Gold II in 3 and Gold III in 1 worker.

Conclusion: Medical triage followed by specific clinical evaluation in a population at risk for silicosis was effective in the early detection of silicosis and yielded a high percentage of COPD. The results stress the need for exposure measures in the tile production industry.


P4935 Chest CT screening of asbestos exposed workers in the Arsenal of Brest: Prevalence of asbestos related lesions and incidental findings
Anne Pégorié1, Nicolas Paleiron1, Thomas Erasco1, Cecile Troumèr1, Sophie Herry1, Yvan Bec2, Bertrand Bouard3, Frédéric Grassin3, Michel Andéol1
1Service de Médecine de Prévention, DCNs, Brest, France; 2Service de Médecine de Prévention, DCNs, Brest, France; 3Centre de Medecine de Prévention, La Villeneuve, Brest, France

Introduction: Chest CT screening is part of the recommendations of the French medical surveillance program of asbestos exposed workers, and seems to have short-ened the delay in the diagnosis of asbestos related diseases, yet conversely to have increased the number of complementary examinations due to incidental findings.

Aims and objectives: The aims of the study were to identify, lung lesions and incidental findings discovered during chest CT screening of asbestos exposed workers, assess the number of lesions considered to be professional diseases, and assess the benefits of incidental findings. The impact of tobacco smoking and the level of exposure were assessed.

Methods: It is a retrospective, analytical study on medical records and chest CT scans of 339 asbestos exposed workers who underwent a first chest CT scan between January 2006 and June 2008, indicated by the health department of Brest military arsenal.

Results: 22% had normal chest CT scans. 54% had pulmonary nodules of which two proved to be malignant. 8.8% had pleural plaques. 3% had dense sub pleural lines. Smokers have twice as many lesions as nonsmokers. No significant difference was shown between patients with different levels of asbestos exposure. On the whole, 9.4% of the images could be related to asbestos exposure. Findings were incidental in 87.6% of cases. They were considered clinically significant in 6 cases.

Conclusion: The diagnosis of few asbestos related lesions and conversely a large amount of incidental findings raise the question of the benefits of a large scale chest CT screening. Indeed, the study highlighted more of a personal, than a medical benefit.

P4936 Asthma and exposure to quaternary ammonium compounds in healthcare settings
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An increased incidence of asthma was reported among professionals working in healthcare settings.

900s

511. The work environment in the clinic

P4934 Medical triage for early detection of silicosis in a ceramic tile production plant
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Objective: Dust containing crystalline silica may cause silicosis, COPD and lung cancer even at low exposure levels. Since no therapy for silicosis is available, early detection is needed to avoid further exposure and progression of the disease. In the Netherlands a national surveillance programme including medical triage has been implemented to identify construction workers with silicosis. For that purpose a diagnostic model has been developed to predict the probability of silicosis by use of a short questionnaire and lung function [1]. In this study medical triage was applied in a ceramic tile production plant.

Methods: The diagnostic model was tailored to the company using historical exposure data. Of a total of 391 workers 353 (90%) participated in the study, 52 of whom (15%) had a high risk (sumscore ≥ 5) and were candidate for medical evaluation, including a low-dose high resolution CT-scan of the lungs.

Results: 48 of 52 workers (response 92%) were referred for clinical evaluation. Mean age was 52 (±5) yrs, number of pack years 28 (±21). Silicosis was found in 8 workers (17%), another 3 in a new number of micromodules on CT (6%). In addition, COPD was present in 6 workers (13%): Gold I in 2 (one of whom had silicosis), Gold II in 3 and Gold III in 1 worker.

Conclusion: Medical triage followed by specific clinical evaluation in a population at risk for silicosis was effective in the early detection of silicosis and yielded a high percentage of COPD. The results stress the need for exposure measures in the tile production industry.

healthcare settings. However the role of the quaternary ammonium compounds (QUATS) is not yet clear in the induction or aggravation of these symptoms.

Aim: To analyze, among health care settings professionals, the influence of QUATS and irritants exposure on the occurrence of respiratory symptoms including asthma.

Methodology: All workers with more than 6 months of seniority working in 7 healthcare facilities were requested. The survey included a self-administered questionnaire, physical examination, spirometry and blood sample. Occupational exposure assessment was made by expert judgment and workplace studies.

Results: 543 workers participated. QUATS occupational exposure was specified for 335 exposed and 109 non exposed. The QUATS exposed workers were 50% nurses, 22% auxiliary nurses, 19% cleaners. The frequency of all variables defining asthma was significantly higher among the QUATS exposed workers: 18.3% vs 5.5% for ever asthma, 14.4% vs 2.7% for asthma confirmed by a physician, 6.7% vs 1.8% for asthma in the last 12 months, 7.9% vs 1.8% for new onset asthma after entry into healthcare profession. In multiple analysis, after adjustment of variables defining asthma was significantly associated with QUATS exposure increased the risk of asthma, the high-risk tasks being the disinfection of surfaces, the preparation of soaking solutions, the dilution of products and the use of sprays.


Department of Occupational Diseases & Toxicology, Nofer Institute of Occupational Medicine, Lodz; Poland

Work-exacerbated rhinitis (WER) is pre-existing or concurrent rhinitis that is worsened by workplace exposures, while the disease has not been caused by the work environment. WER is currently less well characterized than the corresponding entity of work-exacerbated asthma and exact data on its prevalence and associated factors are usually not known. The aim of the study was to evaluate the frequency of WER in bakers with suspected respiratory occupational allergy.

Material and methods: The study group included 393 bakers reporting respiratory symptoms at the workplace. In all subjects questionnaire, spirometry, skin prick test and evaluation of serum total and specific IgE level were performed. Recognition of occupational rhinitis (OR) was based on inhalative specific challenge test with evaluation of nasal response (nasal lavage analysis).

Results: OR was found in 138 (35.1%) bakers while WER was recognized in 116 (29.5%) subjects. 66.7% subjects with OR and 43.1% with WER had positive SPT to common allergens, while occupational SPT were positive in 76.8% and 33.6% subjects respectively. In patients with OR the latency period, i.e. duration of exposure before the occurrence of symptoms was 10.8 whereas in bakers with WER 13.8 years. Generally, bakers who suffered from occupational rhinitis were younger than the patients with WER. Additionally, OR coexisted with asthma more frequently than WER.

Conclusions: WER is frequent health problem and concerns about 30% of bakers reporting allergic respiratory symptoms. Its differentiation with OR should include specific challenge test, as anamnesis, skin prick tests to total serum level of specific IgE. Recognition of occupational rhinitis (OR) was based on inhalative specific challenge test with evaluation of nasal response (nasal lavage analysis).

Diagnoses and frequency of work-exacerbated asthma among bakers Marta Wisniewska, Agnieszka Lipinska-Ojrzanowska, Ewa Nowakowska-Swirta, Patrycja Krawczyk-Srul, Cezary Palczynski, Jolanta Walasiuk-Skorupa. Department of Occupational Diseases & Toxicology, Nofer Institute of Occupational Medicine, Lodz; Poland

The term work-exacerbated asthma (WEA) refers to asthma that is worsened by workplace exposures. The aim of the study was to evaluate the frequency of WEA in bakers reporting work-related respiratory symptoms and the usefulness of allergologic tests in differentiating WEA and occupational asthma (OA).

Material and methods: The study group included 393 bakers. In all subjects questionnaire, spirometry, SPT, evaluation of total and specific IgE level were performed. Recognition of OA was based on inhalative specific challenge test with evaluation of bronchial response or a threefold increase in non-specific bronchial hyperreactivity accompanied by increase sputum eosinophilia.

Results: Occupational etiology of asthma was found in 44.5% bakers while WEA was recognized in 16% subjects. 60% subjects with OA and 50.8% with WEA had positive SPT to common allergens, while occupational SPT were found in 74.9% and 34.9% subjects respectively. Whereas specific IgE to flores were found in 6% of bakers with OA and 28.6% with WEA. In patients with OA the latency period was 11.2 years whereas in bakers with WEA 13.3 years. Additionally, OA frequently coexisted with occupational rhinitis (53.7%) while among bakers with WER rhinitis was found in 31.7% subjects.

Conclusions: WEA can be diagnosed in 16% of bakers reporting allergic respiratory symptoms. The specific challenge test with occupational allergens should be performed among bakers with suspicion of work-related asthma, because assessment of increased (SPT to occupational allergens, evaluation of specific IgE) is not specific enough to differentiate occupational and work-exacerbated asthma.
P4941

A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma

Vicky Moore1, Marietta Jakkola2, Sherwood Burge1. 1Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Birmingham, United Kingdom; 2Respiratory Medicine Unit, Oulu University, Oulu, Finland

This work systematically reviews literature on the application of serial peak expiratory flow (PEF) measurements in the diagnosis of occupational asthma (OA) and calculates summary estimates of the sensitivity, specificity and feasibility of serial PEFs.

**Methods:** Papers were searched for on the Medline database via the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) and on the Birmingham Chest Clinic departmental website www.occupationalasthma.com from 2004 until April 2009 using the search terms “Peak flow AND occupational asthma” and “Peak flow AND work related asthma.” Abstracts were screened to select those justifying a full paper review. Papers used in the British Occupational Health Research Foundation (BOHRF) guidelines (current until June 2004) were also reviewed. Case studies and narrative reviews were excluded. Type of analysis, quality of paper, sensitivity and specificity of PEFs compared to reference tests and return rates were documented. Results were pooled from all studies to produce overall estimates.

**Results:** A total of 80 abstracts were reviewed, leading to 23 full papers plus 15 papers from the 2004 BOHRF review. 7 papers were excluded. The pooled sensitivity of serial PEF fulfilling minimum data quantity requirements for a diagnosis of OA was 82% (95% CI 76-90) and the pooled specificity 88% (95% CI 80-95). Return rates were similar between PEFs requested through workplace studies (85%) and those requested in a clinical setting (78%).

**Conclusion:** Based on a systematic literature search, serial PEF measurement is a feasible, sensitive and specific test for the diagnosis of OA, when potential sources of error are understood.

P4942

FEV1 decline and eosinophilia in occupational asthma

Donatella Talini1, Federica Novelli2, Elena Bacci2, Marta Laura Bartoli2, Silvania Ciocchetti1, Federico Lorenzo Dente2, Antonella Di Franco2, Lorenza Melosini2, Pierluigi Paggiaro2. 1Prevention Department, Occupational Health Unit, Pisa, Italy; 2Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy

**Background:** There are few informations available on how rapidly lung function declines in subjects with occupational asthma (OA) who continue to be exposed.

**Subjects:** We monitored 38 subjects with OA (age 41.9±11.7 yrs, 4 smokers and 19 ex-smokers). 16 (44.1%) were exposed to high molecular weight compounds (HMWC) and 22 (57.9%) to low molecular weight compounds (LMWC), with an occupational exposure of 16.0 (range: 1-45) yrs. We used simple regression analysis to provide estimates of the decline in FEV1 during the period of occupational exposure 4.1 (range 1.2-13.7) yrs. The mean rate of change in FEV1 was −32.9 (range: -217.31-426.2) ml/yr.

**Results:** In all subjects FEV1 decline was significantly worse (*p*=0.04) in subjects with higher eosinophilia (>3%), but there wasn’t difference between subjects exposed to LMWC or HMWC not respect to the use of inhaled corticosteroids (ICS). Compared with controls, FEV1/5 pred at baseline and follow-up visit showed significant improvement only in subjects with lower eosinophilia (91.9±17.5 vs 96.6±15.7, *p*=0.01). Logistic regression analysis (mean annual change in FEV1 < than median value −32.9 ml/yr as dependent variable) was performed.

**Conclusion:** Baseline FEV1 and sputum eosinophilia are both determinants of a more rapid FEV1 decline in patients with OA still exposed in the workplace.

P4943

Pulmonary toxicity in car spray painters

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**Background:** Spray painters comprise a large population at risk with potentially high isocyanate exposure. Repeated pulmonary function testing is not sufficient to diagnose and evaluate pulmonary toxicity induced by car paint sprays. Therefore Clara cell secretory protein (CC16) was selected as a sensitive marker of bronchial tree injury.

**Methods:** The study involved 50 workers exposed to isocyanates during car spray-painting; in addition to 30 control subjects. All participants were subjected to pulmonary function testing, bronchoscopy and lavage, and serum CC16 estimation.

**Results:** Different pulmonary function indices as well as CC16 serum levels were found to be significantly decreased in the exposed group. Clara cells were markedly damaged in the exposed subjects, whereas smokers exhibit excessive epithelial cells desquamation.

**Conclusions:** In this study clear associations between lung function parameters, CC16 serum levels, and exposure to isocyanate-containing paint-sprays were demonstrated. This stresses the importance of regulation and control of such exposure. Also, assay of serum CC16 could be used to detect pulmonary toxic effects.

P4944

Is diurnal PEF variation sensitive and specific for the diagnosis of occupational asthma?

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Serial peak expiratory flow (PEF) measurements on days at and away from work are recommended as the first step in the objective confirmation of occupational asthma. This study aims to identify the best cut off for the difference between diurnal variation (DV) at work and DV at rest (days off work) that is both sensitive and specific for diagnosing occupational asthma.

**Methods:** Mean 2-hourly PEFs were plotted separately for work days and rest days for 109 workers with occupational asthma and 117 control asthmatics. DV at work and rest was calculated by the Oasys program from records containing ≥ 4 day shifts, > 4 rest days and ≥ 6 readings per day. DV at work minus DV at rest was calculated by% predicted and% mean. Patients were randomly divided into 2 datasets (analysis and test sets). Receiver operator characteristic curve analysis determined a cut off point from Set 1 that best identified those with occupational asthma, which was then tested in Set 2.

**Results:** ROC curve analysis gave an area under the curve of 0.68 (set 1) and 0.69 (set 2) analysed as% mean and 0.70 (set 1 and set 2) analysed as% predicted. Table 1 shows the sensitivity and specificity of DV at different cut offs in set 2.

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<th>Set 2: DV at work – DV at rest (%) predicted</th>
<th>Set 2: DV at work – DV at rest (%) mean</th>
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<td>Sensitivity (%)</td>
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<tr>
<td>0.6</td>
<td>67</td>
</tr>
</tbody>
</table>

**Conclusion:** A 1.4% higher DV at work compared to rest has the best combined sensitivity and specificity for the diagnosis of occupational asthma. Although the sensitivity and specificity are acceptable, they are somewhat lower than other scores generated by the Oasys program.
P4945
Airway symptoms and lung function among male workers in the aftermath of an oil tank explosion
Jens-Tore Otniel1, Bjørg Eli Holland1, Ågot Irgens1, Magne Bråtveit1, Cecilia Svanes1, Bente Elisabeth Moen1,2, 1Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway; 2Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

Background: In 2007 storage tanks with a heterogeneous mixture of hydrocarbons, sulphur compounds and hydrochloric acid exploded and caught fire in a Norwegian industrial harbour. Pollution in air and soil produced an intense smell until clean up was terminated in 2009. Respiratory symptoms and lung function was assessed 1.5 years after the explosion among male fire-fighters, clean-up workers, and employees working in the industrial harbour at the time of the accident. Methods: 163 exposed men (fire-fighters, clean-up workers, and local employee at the time of the accident) (response rate 86%) and 90 male controls (home address >20 km from the accident place), aged 18-67 years participated with a questionnaire and spirometry (response rate 59%). Regression analyses of the relationship between outcomes and exposure were performed, adjusting for smoking, occupational exposure matrix, Phadiatop® status, infection last month, and age (symptoms).

Results: Exposed men reported more daily cough; odds ratio 2.0 [95% confidence interval 1.1, 3.7]; dyspnoea walking up hill 2.6 [95% CI 1.3, 5.2] and sore throat 2.3 [95% CI 1.1, 4.7]; FEV1% predicted was 89.0 among exposed and 91.1 among controls, adjusted difference -1.9 [95% CI 0.6, 3.2].

Conclusion: Fire-fighters, clean up workers and local employee exposed to air pollution from an oil tank explosion had more airway symptoms than a control group 1.5 years after the accident, but not significantly different lung function.

P4946
Is FEV1 better than PEF at detecting asthmatic changes in diurnal variation? Kersty-Anne Dennis1, Vicky Moore1, Cedd Burge1, Sherwood Burge2
1Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Birmingham, United Kingdom; 2Health and Human Sciences, NIOSH, Morgantown, United States

FEV1 is considered the best measure of airflow obstruction but PEF is more commonly used to diagnose occupational asthma as it’s easier to achieve unsupervised.

We investigated whether FEV1 or PEF was more sensitive at identifying asthmatic variation when compared to EMG variation, and whether there were differences in interpretation. The aim was to confirm validity of serial PEF examinations in model study of bronchial obstruction in exposed and control group.

Methods: 14 asthmatics from the USA and 84 from the UK were studied. The USA group used the Easyone and the UK group the Piko-l, Vitallograph 2110, or Aparatec 1000. The workers were exposed 16 times, tested under similar conditions and had weekend rest days. The study was continued for at least 2 weeks with the occupational asthmatic records also having 10 day shifts.

Within session PEF and FEV1 variation was assessed for the USA data (as the months progressed, better attempts) using a coefficient of variation (COV). Diurnal variation% predicted (DV) was analysed for all data. Timepoint analysis (an Oasys program scoring system for occupational asthma) was performed on occupational asthmatics.

Results: The table below compares COV and DV for PEF and FEV1 (SD-standard deviation).

<table>
<thead>
<tr>
<th>PEF mean (SD)</th>
<th>FEV1 mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COV (USA)</td>
<td>8.05 (1.86)</td>
<td>5.67 (1.88)</td>
</tr>
<tr>
<td>DV (USA)</td>
<td>15.51 (9.05)</td>
<td>12.43 (7.81)</td>
</tr>
<tr>
<td>DV (UK)</td>
<td>17.81 (7.51)</td>
<td>16.26 (8.35)</td>
</tr>
<tr>
<td>DV USA &amp; UK</td>
<td>16.61 (8.49)</td>
<td>14.26 (8.27)</td>
</tr>
</tbody>
</table>

There was no significant difference in the number of day shift positive drops (from Timepoint analysis; a drop signifies a significant difference between work and rest) between FEV1 and PEF (p=0.859) and no difference in the number required to produce a positive drop (p=0.297).

Conclusion: Diurnal variation is significantly greater for PEF than FEV1 in asthmatics with similar within session variation using logging meters incorporating some quality control. PEF is as good as FEV1 for diagnosing (occupational) asthma.

P4947
A quantitative European study to investigate the impact of asthma triggers on the lives of asthma patients
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Background: There is frequent reference to asthma triggers in the patient education literature but little is known of patients’ experiences with triggers and their impact on and relationship to asthma control.

Methods: We used patient diaries and an online study to quantify the impact of asthma triggers in patients from five European countries (France, Germany, Italy, Spain, UK). 1202 asthma patients completed the study; 177 also completed an online diary every other day for 3 weeks.

Results: People with asthma expressed concern about the long term impact of triggers – only 1% believed that triggers would not affect their asthma. All triggers were perceived as having an impact on asthma symptoms (at least 6.1 for all triggers on a 10 point scale). Perceived impact increased with the increasing number of triggers identified by each patient. 80% of respondents claimed to have modified their behaviour due to exposure to triggers at least once in the last 4 weeks. Patients reporting a high number of triggers experienced more day and night-time symptoms, a greater number of severe attacks, had a lower Asthma Control Test (ACT) score, were more likely to be hospitalised and to miss days at work/school. People with asthma experiencing 16 or more triggers missed on average 12.2 days compared with 2.9 days for those reporting 1-5 triggers. Of those patients with a high number of triggers, just 3% had never adapted behaviour to manage their asthma.

Conclusion: Asthma triggers can have an important impact on the lives of asthma patients. The impact increases with the number of triggers experienced and results in significant behavioural changes.

Funded by GSK

P4948
Occupational asthma in two healthcare workers due to an alcohol hand gel
Alastair Robertson, Vicky Moore, Cedric Burge, Marcus Wong, Sherwood Burge
Occupational Lung Disease Clinic, Birmingham Chest Clinic, Birmingham, United Kingdom

Alcohol hand gels are increasingly being used by healthcare workers to reduce the risk of hospital-acquired infection. To date they have not been identified as a risk to healthcare workers. We present two cases of occupational asthma in healthcare workers due to an alcohol hand gel containing a quaternary ammonium (denatonium) biobit agent.

The healthcare workers, a midwife (case 1) and a nurse (case 2), presented with asthma improving on days away from work. Both had developed symptoms in relation to using the same alcohol hand rub. Both workers completed serial peak flow measures which showed occupational asthma (case 1 OASYS score 3.43, case 2 OASYS score 3.93). A series of bronchial challenge tests were performed to the hand gel and a control agent. Case 1 had a dual asthmatic reaction and case 2 had a prolonged immediate reaction to the hand gel. Both workers improved on removal from exposure.

Hand gels containing denatonium are used extensively by healthcare workers. There needs to be an awareness of this agent as a potential cause of occupational asthma in this group of workers.

P4949
Peak expiratory flow monitoring – Optimal criterion for diagnosis of professional asthma?
Environmental Medicine and Clinical Toxicology, Medical Faculty of University of P.J.Safarik, Kosice, Slovakia (Slovak Republic) Respiratory Diseases and Tuberculosis, University Hospital of L. Pasteur, Kosice, Slovakia (Slovak Republic)

Introduction:

Results:

P4945
Massive acute gases intoxication: Clinical presentation and outcomes
María Sánchez-Carpintero Abad⁴, Ana Belén Alcaide⁴, Arazana Camps⁵, Jorge Zagaeta⁶, Felip Lucena⁵, Manuel Lomacho⁵, Felix Alegre⁵, Luis Seijo⁵, Juan Pablo de Torres⁴, Javier Zulueta⁴, ¹Pulmonology, Clínica Universidad de Navarra, Pamplona, Navarra, Spain; ²Internal Medicine, Clínica Universidad de Navarra, Pamplona, Navarra, Spain.

On Oct 30th, 2008, a car bomb exploded on the University of Navarre (UN) campus, causing serious damages and several fires. On Nov 5th, during the repairing works, gases retained inside the fake ceiling were released, causing intoxication by inhalation in about 300 people. A longitudinal observational study was performed to assess the presentation and outcomes of 230 patients assisted at the Emergency Room (ER) of the UN Hospital. Employees and students were affected: 104 men and 126 women, with mean age 31±12 y, 23% smokers and 13% with previous respiratory disease. 65% of patients got to the ER on Nov 5th. At the first 6 h commonest complaints were cough (80%), dyspnea (51%), sore throat (38%), and vomiting (7%). Chest xray (n=218) showed infiltrates in 17.5% and chest CT (n=19) interstitial/alveolar infiltrates in 68%. Blood analysis (n=101) revealed leukocytosis in 65%, and high CRP in 85%. 80 patients were hospitalised (34.8%) with a median length of stay of 1 day (max 5 d). At the ER, patients received bronchodilators (62%) and steroids (54%). Upon discharge, bronchodilators (82%), steroids (30%) and N-acetyl cysteine (82%) were prescribed.

One month after discharge, 206 patients were re-evaluated: 41 (20%) had symptoms, consisting in dyspnea (12%) and cough (11%). Chest CT (n=218) showed infiltrates in 17.5% and chest CT (n=19) interstitial/alveolar infiltrates in 68%. Blood analysis (n=101) revealed leukocytosis in 65%, and high CRP in 85%. 80 patients were hospitalised (34.8%) with a median length of stay of 1 day (max 5 d). At the ER, patients received bronchodilators (62%) and steroids (54%). Upon discharge, bronchodilators (82%), steroids (30%) and N-acetyl cysteine (82%) were prescribed.

Methods: 42 rats were randomly divided into three groups: normal control (NC) group, CIH group and CIH+Ad group with 14 rats in each. Rats in NC group were housed in an air-conditioned room with normal environment. In the CIH group rats received CIH from day 42 until sacrifice and in the CIH+Ad group rats received CIH and adiponectin (Ad) from day 42 until sacrifice. The rats were kept under a controlled light/dark cycle (12h:12h) and had free access to food and water. Body weight and food intake were monitored daily. After sacrifice, rats were sacrificed by decapitation and the lung tissue was collected. Tissue samples were used for histological and ultrastructural analysis.

Results: In the CIH group there was a significant reduction in lung function as compared to the NC group. The histological analysis revealed a significant increase in the number of alveolar septa. The ultrastructural analysis showed a significant decrease in the number of mitochondria per cell. These findings suggest that chronic intermittent hypoxia leads to a decrease in lung function and an increase in the number of alveolar septa.

Conclusion: Chronic intermittent hypoxia leads to a decrease in lung function and an increase in the number of alveolar septa. These findings suggest that chronic intermittent hypoxia leads to a decrease in lung function and an increase in the number of alveolar septa.
**Wednesday, September 28th 2011**

**P4955**  
**Improvement in obstructive sleep apnea features under targeted hypoglossal neurostimulation is independent from body mass index and collar size**

Daniel Rodenstein1, Benny Mwenge1, Myriam Dury1, Benoit Lengle2, Philippe Rembaum3, 1Pneumology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 2Plastic Surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 3ENT, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

**Background:** The treatment of moderate to severe obstructive sleep apnea (OSA) is continuous positive pressure (CPAP) applied during sleep. Although its health effects are beyond doubt, many patients refuse or stop CPAP because of intolerance or local side effects. Alternative therapies are needed.

**Aim:** We used targeted hypoglossal neurostimulation (THN) to treat 11 patients (1 female) non compliant with CPAP with the aim of improving both breathing and sleep.

**Methods:** One hypoglossal nerve was stimulated through a multicontact cuff electrode positioned around the main trunk of the nerve and connected to a stimulator implanted in a subcutaneous pocket on the anterior chest wall. Stimulation was applied continuously during sleep.

**Results:** The BMI of the group was 30.7±3.5 kg/m²; on diagnostic polysomnography and MRI imaging for soft-tissue volumetric measurements.

**Conclusion:** The data strongly suggest that didgeridoo playing decreases the AHI by downsizing parapharyngeal fat pads.

**P4956**  
**Supine position dependency in obstructive sleep apnea**

Selma Pirat Guven1, Bülent Ciftci1, Tanou Utkuak Ciftci2. 1Sleep Disorders Center, Ankara Chest Diseases, Thoracic Surgery Training and Research, Ankara, Turkey; 2Sleep Disorders Center, Faculty of Medicine, Gazi University, Ankara, Turkey.

**Introduction:** It is known that supine sleep position may lead to an increase in the severity of obstructive sleep apnea (OSA) patients. The aim of this study was to define the prevalence of supine positional OSA in patients diagnosed with OSA and to draw attention to alternative therapy planning in these patients.

**Patients and Method:** A total of 3,214 patients diagnosed as OSA between June 2007 and June 2010 were included to the study. Positional OSA was defined as a total apnea-hypopnea index (AHI) 2.5 and supine AHI/supine AHI ≥ 2. Characteristics of positional OSA and non-positional OSA groups were compared statistically.

**Results:** Patients grouped as positional OSA composed 39.9% (n: 1283) of all patients. Positional OSA patients were younger with lower body mass index (BMI) and their OSA was less severe.

**Conclusions:** Positional OSA, which may require different treatment approaches, is not uncommon among OSA patients and should be understood as a different clinical entity.

**P4957**  
**Berlin questionnnaire performance for detecting sleep apnea in the general population**

Raphael Heinzer1,2, Daniela Andries1, Francois Bastardot3, Nadia Tobback1, Raphael Heinzer1,2, Daniela Andries1, Francois Bastardot3, Nadia Tobback1, 1Pneumology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 2Plastic Surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 3ENT, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

**Introduction:** Berlin questionaire (BQ) has been proposed as a screening tool for identifying patients at risk for obstructive sleep apnea (OSA). The aim of our study is to evaluate the performance of this questionnaire for detecting OSA in a large sample of middle-aged general population.

**Methods:** 469 subjects (46.4% women, 50.6±10.0). Prevalence of OSA defined as an AHI >5; ≥ 15 and ≥30 was 33.3%, 10.3% and 3.8%, respectively in our population. Prevalence of positive BQ score was 24% (29.2 in men, 18.1 in women). BQ sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect OSA were 36.1%, 82.4%, 51.8% and 72.9% respectively for an AHI >5; 51.2%, 78.8%, 21.9% and 93.5% for an AHI >15; and 72.2%, 77.6%, 11.4% and 98.6% for an AHI >30. Positive BQ was associated with higher 4% ODI (10.8±4 vs 4.2±0.001), higher Epworth score (8.3 ±6.2 vs 0.0001) and broader neck circumference (38.6 ±35.7 cm vs 0.0001).

**Conclusion:** BQ questionnaire performance for identifying OSA is lower in a middle-aged general population than previously reported in a clinical population. Our results do not support its use as a screening tool for OSA in an unselected population.

**P4958**  
**STOP-BANG score as a screening tool for obstructive sleep apnea in the general population**

Raphael Heinzer1,2, Daniela Andries1, Francois Bastardot3, Nadia Tobback1, Raphael Heinzer1,2, Daniela Andries1, Francois Bastardot3, Nadia Tobback1, 1Pneumology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 2Plastic Surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 3ENT, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

**Introduction:** STOP-BANG (Scoring Tiredness during daytime, Obesity, Hypertension, Blood pressure, Male, Age >50, Neck circumference >40 cm, Gender score has been shown to be a useful tool to screen for obstructive sleep apnea (OSA) during preoperative evaluation. The aim of our study is to evaluate the mean STOP-BANG score in a large sample of middle-aged general population.

**Methods:** 458 subjects (47.7% women, 50.6±7.5 years old, BMI 25.2±4.9 kg/m²) participating in an ongoing population-based cohort study (HypnoLaus, Lausanne, Switzerland) underwent a complete polysomnographic recording at home and an extensive clinical workup including BQ. This instrument includes 3 categories: 1) witnessed apnea and snoring 2) daytime sleepiness and 3) obesity or hypertension. A positive score in 2 or more categories was considered suggestive of OSA.

**Results:** Mean AHI was 6.3±10.6. Mean 45°ODI was 5.8±10.0. Prevalence of OSA defined as an AHI >5; ≥ 15 and ≥30 was 33.3%, 10.3% and 3.8%, respectively in our population. Prevalence of positive BQ score was 24% (29.2 in men, 18.1 in women). BQ sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect OSA were 36.1%, 82.4%, 51.8% and 72.9% respectively for an AHI >5; 51.2%, 78.8%, 21.9% and 93.5% for an AHI >15; and 72.2%, 77.6%, 11.4% and 98.6% for an AHI >30. Positive BQ was associated with higher 4% ODI (10.8±4 vs 4.2±0.001), higher Epworth score (8.3 ±6.2 vs 0.0001) and broader neck circumference (38.6 ±35.7 cm vs 0.0001).

**Conclusion:** BQ questionnaire performance for identifying OSA is lower in a middle-aged general population than previously reported in a clinical population. Our results do not support its use as a screening tool for OSA in an unselected population.

**P4959**  
**AutoCPAP devices accurately identify obstructive sleep apnea patients with residual apnea during treatment**

Lena Hess, Tsygadal D. Latsang, Malcolm Kohler, Christian M. Lo Cascio, Robert Thumber, Konrad E. Bloch. Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland.

**Background:** Objective data on the effectiveness of CPAP therapy of patients with obstructive sleep apnea syndrome (OSA) are needed. The accuracy of the apnea/hypopnea index (AHI) recorded by CPAP devices during treatment is unknown. We tested the hypothesis that AHI derived from CPAP devices accurately predict an elevated AHI during a sleep study.

**Methods:** 48 patients, mean±SD age 54.6±5.9, baseline AHI 52.5±21.6, underwent in-laboratory sleep studies once or twice during long-term autoCPAP therapy. AHI from CPAP devices (RespMed S8, Philips Respironics REMstar) during sleep studies and during the preceding 7 nights were recorded.

**Results:** The AHI derived from 60 sleep study was 5.0±6.2. The mean difference (bias) of the corresponding AHI from CPAP devices was 1.8±8.9. 95% confidence interval 7.4±11.0. The difference between the minimal and maximal CPAP-derived AHI in the week preceding the sleep study was 6.1±5.1. In
22 of 60 sleep studies, the AHI was >5/h. The accuracy of the AHI from CPAP devices to correctly predict an elevated AHI (>5/h) was quantified by the area under the receiver operating characteristic curve of 0.87 (95% CI 0.78 to 0.96). The sensitivity and specificity of an AHI >5/h from CPAP devices to identify a polygraphic AHI >5/h were 86% and 75%, respectively; the negative and positive predictive values were 95% and 56%, respectively.

Conclusions: The studied CPAP devices accurately identify OSA patients with elevated AHI during treatment. Because of the high night-to-night variability mean AHI derived from autoCPAP devices over several nights might be clinically more relevant than a single night AHI measured in the sleep laboratory.

Methods: We recruited consecutive sleep referrals over a 5 month period. We compared the total and average time taken with this algorithm to perform a screening (control arm) of LCSS for every patient. The study was powered for 50 patients, 30 had been recruited to date.

Results: N=30. Median age 53 years, 19 were male. See table for results; average time saving - 24.5 minutes per patient.

Conclusion: We propose that allocating high probability subjects to oximetry and using LCSS for low probability subjects and for oximetry negative high probability subjects results in significant time and resource savings.

References:

Methods: We studied 289 children (6.5 ± 3.1 yrs, 63.3% M). We found 28% children had lower AHI than OSAS' children with positive score (5.1 ± 3.1, p < 0.005) and it was correlated with AHI (r=0.156, p=0.008). The SCS’s distribution has identified the value of 6.5 as its 25th centile, so the SCS was defined as positive when it was major of 6.5. The SCS was positive in 224 of the 289 children studied, of these 177 had OSAS (real positives) and 47 were PS (false positives). 65 children was major of 6.5. The SCS was defined as positive when it

Conclusions: The proposed method represents a valuable screening tool that could contribute to reduce the number of required PSG tests.

Aims: To develop a reliable tool, PSG validated, for diagnosis of SDB and to reduce the use of PSG.

Methods: Children with referred SDB undergoing a PSG for the first time. We proposed the Sleep Clinical Record (SCR) to predict SDB in children, based on clinical experience. It consists of objective data, subjective symptoms, clinical history, behavioural and cognitive problems. These items were used in a model which combine subjective and objective parameters to create the sleep clinical score (SCS) with the higher predictive value.

Results: We studied 289 children (6.2 ± 3.1 yrs, 63.3% M). We found 28% children’s with primary snoring (PS) and 72% with OSAS. The SCS was higher in children with OSAS than children with PS (8.9 ± 2.7 vs 7 ± 4.3, 1 < p < 0.005) and it was correlated with AHI (r=0.156, p=0.008). The SCS’s distribution has identified the value of 6.5 as its 25th centile, so the SCS was defined as positive when it was major of 6.5. The SCS was positive in 224 of the 289 children studied, of these 177 had OSAS (real positives) and 47 were PS (false positives). 65 children had a negative SCS, of these 31 were diagnosed as OSAS (false negatives). These children had lower AHI than OSAS’ children with positive score (5.1 ± 4.9 vs 8.9 ± 10.1, p = 0.04).

Conclusion: This SCS is useful to screen SDB in selected population with referred symptoms, and is able to perform diagnosis of OSAS with a positive predictive value of 79% and an accuracy of 73%. It is a useful tool to select patients with OSAS that could be treated without PSG diagnosis when the study is difficult to perform or is unavailable.

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Introducing Chest with selected full paper presentations — Wednesday, September 28th 2011

906s
**Results:** Apnea-hypopnea index (AHI) of SleepMinder correlated well with PSG-AHI on simultaneous application (r=0.90, p<0.001). For PSG-AHI cut-off >15/h and SleepMinder-AHI cut-off >13.4/h, sensitivity was 77.3% and specificity was 100%. Furthermore, SleepMinder correlated with PSG regarding total sleep time (r=0.59, p=0.001), sleep efficiency (r=0.49, p<0.006) and time to sleep (r=0.41, p=0.03).

**Conclusions:** This study showed that SleepMinder, a non-contacting screening device, detects sleep apnea with sufficient diagnostic accuracy. Moreover, SleepMinder correlates with total sleep time, sleep efficiency and time to sleep.

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**Introduction:** SleepMinder correlates with total sleep time, sleep efficiency and time to sleep. Moreover, SleepMinder detects sleep apnea with sufficient diagnostic accuracy. Hence, SleepMinder can be used as an adjunct to polysomnography (PSG) in a sleep laboratory.

**Methods:** 69 unselected subjects (20 – 73 yo) referred to a sleep laboratory for PSG complaining of SD-DS participated. No attempt was made to select patients with asthma or chronic cough. PSG by standard methods and ARM (Pulmotrack, KarmelSonix, Haifa, Israel) were adequate for all but 3 patients (5%). The analysis was done minute by minute throughout the record where Wz=rate occupied by Wz and C coughCOUNT (CC) were measured. The present study concerns the detection of nocturnal Wz and C by ARM without reference to the PSG data.

**Results:** The duration of the overnight ARM in the 66 subjects was 65 – 478 min (median 439 min). Wz-minutes, defined as the number of minutes with a Wz% 5% and C-minutes, the number of minutes with CC>1 were determined. In 16/66 (24%) of patients Wz-minutes occupied more than 3% of the recording and in 29/66 (10.6%) C-minutes occupied more than 2% of the recording with overlap in 3 patients who had both Wz and C.

**Conclusion:** With 20/66 (30%) of unselected patients referred to an adult sleep laboratory because of SD-DS might be suffering from nocturnal Wz or C.

**Discussion:** There is an expectation that scorers can accurately distinguish obstructive from central events. This observational study shows that interpretation varies widely. This has important consequences for treatment of individuals and for conduct of research studies. AASM rules may provide more clarity and improve concordance but ongoing training and interlaboratory comparisons are essential.

**Results:** The ASI technique was found to enable recognition of subjects classified as central or mixed for each scorer and each study. A superimposed box plot shows median, 25th and 10th percentiles.
P4969
A case-control study of the risk of adverse peri-natal outcomes due to tuberculosis during pregnancy
Bassey Asuquo1, Arun Vellore2, Gareth Walters3, Heike Kunst1,2 Department of Respiratory Medicine, Queen Elizabeth Hospital, Woolwich, London, United Kingdom; 1Department of Respiratory Medicine, Birmingham Heartlands Hospital, Birmingham, West Midlands, United Kingdom

Aim: The West Midlands, UK has seen a persistent rise in cases of tuberculosis (TB) in immigrants, and TB in pregnancy is more common amongst recent migrants to a country. Diagnosis is often delayed due to non-specific, late presentation, and this has been associated with prematurity and low birthweight (LBW). We aimed to determine the risk of adverse peri-natal outcomes in women with TB in pregnancy.

Methods: A case-control study was conducted at three hospitals in Birmingham, comparing pregnant women with TB (n=204; n = 24) with healthy pregnant controls (n=72). Data concerning the course of pregnancy, birthweight and prematurity were collected from review of case notes. Healthy controls were matched for age and socio-economic status. Urivariate analyses of low birthweight and prematurity were undertaken, and a multivariate regression model constructed to explain differences by ethnicity and prematurity.

Results: Estimated incidence of TB was 62/100,000 pregnancies. 54.2% cases were pulmonary TB (41.7% extra-pulmonary: 4.2% both). Infants of mothers with TB had significantly lower mean birth-weight compared to controls (2760g vs. 3140 g; p=0.028). Mean birth weight was lower in pulmonary TB than in extra-pulmonary TB. Multivariate analysis explained LBW by prematurity (p<0.001) but not ethnicity (p=0.19).

Conclusion: Pregnant women with TB are at higher risk of LBW infants. This is particularly true of mothers with pulmonary TB. Mean duration of symptoms was 8.3 weeks and LBW is attributed to late presentation. Indeed patients have mild symptoms that are confused with those of pregnancy. Therefore a high index of suspicion and early referral and diagnosis is recommended.

P4970
Pregnancy: A risk for developing tuberculosis? A national cohort and self-controlled case series study using UK primary care data

Introduction: Tuberculosis (TB) incidence has increased in the UK over the last decade. The study of TB in pregnancy is important because of adverse outcomes in mother and child. The aim of this study was to analyse the epidemiology of TB in pregnancy in the UK, and establish, whether pregnancy is an independent risk factor for TB in order to inform prevention and early detection strategies.

Methods: Using a cohort based on the UK General Practitioner Research Database (GPRD), incidence rates (IR) and rate ratios (RR) of TB events in three time periods were compared using Poisson regression: pregnancy, a period of 6 months post-partum, and outside of pregnancy. In addition TB risk was calculated using a nested self-controlled case series (SCCS) analysis which implicitly adjusts for time-bounds covariates.

Results: Combined pregnancy and post-partum TB rates (15.4 per 100,000 person years, py) were significantly higher than rates outside of pregnancy (9.1 per 100,000 py, p=0.02). Compared to risk outside of pregnancy, TB risk was not significantly increased during pregnancy (IRR 1.95, CI 1.24-3.07), adjusting for age, region and deprivation. These observations were confirmed in the SCCS (IRR 1.62, CI 1.01-2.58 and 1.03, CI 0.64-1.65).

Conclusion: There is a significantly increased post-partum TB risk and this is very likely pregnancy-related, but occurs post-partum due to administrative, diagnostic or immunological delays. Our results can be used to raise clinicians awareness and inform targeted public health policy measures to minimise this risk.

P4971
Knowledge and attitudes about tuberculosis among non-medical students in University of Novi Sad, Serbia
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Introduction: Students’ knowledge and opinion about tuberculosis (TB) are very important for recognizing early symptoms and signs of disease, prevention of late in diagnosis of TB and influence on prevention and outcome of disease.

Goal: To define the non-medical students’ knowledge about TB (symptoms, way of medical treatment, possible complications, comorbidity).

Material and methods: Prospective study comprised the non-medical faculties at the University of Novi Sad, Serbia. The data were obtained by the questionnaire filled in during October-November 2010.

Results: The total of 1139 students were questioned, average 19.7 year, most women (n=794, 69.7%). The majority of students had a good knowledge about TB (n=991, 78.2%). The majority of questioned students knew that TB is infectious disease (n=1093, 96%) that the main cause of TB is bacteria (n=887, 77.9%) as well as it is curable disease (n=1079, 95.6%). Over 94% knew that cough is the main cause of TB transmission. 62% questioned students considered that risk factors can contribute the tuberculosis appearance (39.4% alcoholism, 66.3% poor nutrition, 74.7% smoking and 67.9% comorbidities). The students from Agricultural faculty showed better knowledge against other students, p<0.001. The most of the students (n=533, 45%) knew that TB incidence in the state area was decreasing.

Conclusion: Students of non-medical faculties at the University of Novi Sad showed the good knowledge about TB. The best knowledge was noticed at the students of Faculty of Agriculture. They also are well informed about TB presented in the state and the effects of national and international guidelines implementation in the country respectively.

P4972
Evaluation of tuberculosis diagnostic criteria in children
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Objective: In this study we reviewed the diagnostic criteria for tuberculosis on 198 children diagnosed with TB

Material and methods: A cross-sectional, descriptive study was conducted on a series of 525 children aged 1 to 15 years. Among 525 patients, 198 were diagnosed with TB. Date of the study were collected from the patients records, chest radiographs and laboratory examinations. Demographic and diagnostic characteristics of patients were reviewed by means of the available criteria.

Results: In this study 38.9% of patients were male and 61.1% were female. Among all patients 34.5% were Iranian and 65.2% were Afghan. In this study 82.8% of patients reported close contact with TB. All patients had pulmonary and extrapulmonary tuberculosis, 72.7% had pulmonary tuberculosis and 14.1% had pulmonary and extrapulmonary involvement.Frequency of TST, contact, clinical symptoms, radiograph findings and bacteriology as diagnostic methods was 79.5%, 83.8%, 83.8%, 95%, and 58.1%, respectively. Due to our setting, 90.4% of patients fulfill the criteria.

Discussion: The result of this study indicate the high diagnostic value of smear and culture of gastric aspirate in children.How ever, it couldn’t be considered as a gold standard for diagnosis of TB in children. In addition the significant accuracy of the available criteria was determined and it could be considered as an efficient diagnostic setting in childhood TB diagnosis.

P4973
Neonatal tuberculosis and cardiac inflammatory myofibroblastic tumor presenting as supraventricular tachycardia: A rarity of kinds
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This a case of a month old female neonate who was admitted for respiratory distress. On admission, electrocardiogram showed supraventricular tachycardia. A 2-D echo showed a mass anterior to the left ventricle and the right ventricular outflow tract (RVOT). Chest radiograph showed a left upper lung haziness and computed tomography (CT) scan of the chest showed a non calcified anterior mediastinal mass with central enhancement. Intramyocardial mass biopsy revealed a large anteriorly located intramyocardial mass covering the RVOT, the great vessels and a portion of the right atrium. Final histopathology result revealed inflammatory pseudotumor, myofibroblastic in nature. Smooth muscle actin (SMA) was positive in many localized spindle cells indicative of their myofibroblastic nature while histiocytic markers- CD68 and S100 were both negative. Because of a high index of suspicion, a tuberculous work-up was done which showed that the patient was positive for tuberculin test (18mm in diameter). Contact screening revealed 3 of the 6 household contacts were positive for pulmonary tuberculosis. Patient was started on anti-tuberculosis medications and on the fifth month of treatment, the patient was asymptomatic, growing well and the mass regressed in size by 50%.
As in adults, occurrence of children TB has become quite rare in the last decades in Italy. We report a survey of 269 consecutive cases of mycobacterial disease (MD) in subjects under 18 years of age, diagnosed or referred to the Regional TB Ref Centre from 2000 to 2010.

**Results:** 139 were M, 130 F, 113 were Italians, 156 immigrants, 135 children received antituberculosis treatment in 2010. Most of these children were with active TB. Treatment and the supervision of child’s tuberculosis. Most children of different ages are infected by household contacts with active tuberculosis, especially parents or their relatives. Children exposed to adults with pulmonary tuberculosis or a positive sputum have a high risk for infection, and the risk increases with the degree of contact.

**Methods:** This is a retrospective study which gathered the 22 children with tuberculosis and AARB smear-positive sputum have a high risk for infection, and a high risk for contact with TB cases, histological results or immunologic tests (IGRA/TST).

**Background:** The family and socioeconomic environment influence the appearance, treatment and the supervision of child’s tuberculosis. Most children of different ages are infected by household contacts with active tuberculosis, especially parents or their relatives. Children exposed to adults with pulmonary tuberculosis or a positive sputum have a high risk for infection, and the risk increases with the degree of contact.

**Methods:** This is a retrospective study which gathered the 22 children with tuberculosis and AARB smear-positive sputum have a high risk for infection, and a high risk for contact with TB cases, histological results or immunologic tests (IGRA/TST).

**Results:** Of the isolated NTM 25 were M, 3 M intracellulare, 2 M. scrofulaceum, 1 M. fortuitum, 1 M. malmoensis, 1 M. Haemophilum, 1 M. Kansasi, 1 M. Xenopi 1 M. Lentiflavum e 4 M. could not be identified. Medical, surgical or combined therapy guaranteed success in 239 pts, 2 had to stop treatment for adverse events, % were transferred to other centres, 3 were lost to follow-up and 20 are still under treatment.

**Conclusion:** Child’s tuberculosis and the socioeconomic environment stop treatment for adverse events, % were transferred to other centres, 3 were lost to follow-up, and 20 are still under treatment.

**Results:** Only 61% showed up for the follow-up examination. Being treated for active TB was a positive predictor for attending follow-up. OR: 0.24, CR: (0.12-0.50), p-value = 0.001. Receiving money for the transport to the hospital was a positive predictor for attending follow-up. OR: 0.068 and CR: (0.001-0.060). P-value = 0.001. Limited financial resources and poor communication are issues related to poor adherence.

**Conclusion:** Patients lost to follow-up is a significant problem. We found, that receiving money for the transport to the hospital is crucial for patient adherence. Children with active TB had a significant higher frequency of attending follow-up. All TB patients attend the TB clinic at the hospital frequently, which could explain the better adherence to follow-up.

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**Methods:** We included 11 BCG vaccinated children younger than 5 years with LTBI. The commercial IGRA (QuantiFERON TB Gold In- Tube®, QFT-GIT), Cultiolis Ltd, Carnegie, Australia was performed two times, before and at 6 month chemoprophylaxis. The cut-off value for positive findings of IGRA was ≥0.35 kIU/L. The TST was performed using 2 IU (0.1 mL) of purified protein derivative tuberculin PPD RT 23 SSI (Statens Serum Institut, Denmark) according to the Mantoux method and transverse diameter of the induration was measured after 72 hours.

**Results:** IGRA values were 8.87±2.01 kIU/L and 8.02±1.99 kIU/L before and after chemoprophylaxis, respectively, which suggests a slight, insignificant decrease (p=0.89). There was no significant difference in PPD values before (12±2 mm) and after (14±2 mm) the treatment, p=0.50.

**Conclusions:** Although the prophylaxis was used, both IGRA and PPD values, remained elevated during the period of 6 months in children with LTBI. Further research is needed to clarify the role of serial IGRA in children up to 5 years.

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Contact tracing among the classmates of a 15 year old smear negative pulmonary tuberculosis
Nooshin Bayat1, Afshin Khajelahai2, Mohammad Reza Boloorsar3, Nazarin Parsanejad. Pediatric Respiratory Disease Research Center, Shahid Beheshti University, Tehran, Islamic Republic of Iran; Pediatric Respiratory Disease Research Center, Shahid Beheshti University, Tehran, Islamic Republic of Iran; Pediatric Respiratory Disease Research Center, Shahid Beheshti University, Tehran, Islamic Republic of Iran

Objectives: This study aimed to identify the infected or disease cases among contacts of the 15 year old girl with smear Negative pulmonary tuberculosis in an school outbreak and establish prophylaxis and treatment needed.

Methods: 52 contacts were screened by a tuberculin skin test and Chest X ray initially. Those children who had either a positive PPD or an abnormal chest X-ray were candidate for a tripled Gastric washing (Smear, Culture, Polymerase chain reaction (PCR)) and a Chest spiral CT scan.

Results: 20 contacts (38%) were considered as an infected due to either positive TST or abnormal Chest X-Ray. 28% had a positive Tuberculin Skin Test. Consequently 3 (5.7%) cases of active TB were identified through our investigations.

Conclusion: Our study suggest that even children with TB, who may have a negative smear, can transmit infection to others and therefore should be considered infectious until proven otherwise and contact tracing should be considered for contacts of all symptomatic pulmonary tuberculosis children.

Interferon-gamma release assays (IGRA) for latent tuberculosis infection (LTBI) in children
Rizwan Ahmed1, Deborah Gascoyne-Binzii2, Sandy Moffitt3, Timothy Collyns4, John Watson5,1 Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 2Department of Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Background: IGRA, QuantiFERON®-TB Gold in-tube (QFT-GIT) & T-SPOT.TB®(T-Spot), are widely used to detect LTBI in adults. There is paucity of data regarding their use in children (<16 yrs old), but their use in this group is increasing [1]. One of the key reported problems in children is high incidence of indeterminate results. Studies in adults have shown this can be minimized with early incubation of QFT-GIT blood samples. In Leeds there is close co-ordination between medical & nursing staff collecting bloods, and the local laboratory processing them with prompt transport of samples and the aim to incubate samples within 4 hours of collection.

Methods: We retrospectively reviewed all the IGRA tests performed in children, for contact & new entrant screening, in our TB service between 2008 & 2010, to look at our indeterminate rates.

Results: A total of 188 IGRA tests were performed. T-Spot was undertaken almost exclusively in children under 1 year. None of our cohort had indeterminate IGRA results with QFT-GIT or T-Spot.

Table 1

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Number of tests performed</th>
<th>Indeterminate Results</th>
<th>Negative tests</th>
<th>Positive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTG-GIT</td>
<td>5</td>
<td>19</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>5-10</td>
<td>39</td>
<td>0</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>111</td>
<td>0</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>T-Spot</td>
<td>&lt;5</td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>5-10</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>All &lt;16</td>
<td>188</td>
<td>0</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>

None of the children were diagnosed with active TB (multiple samples were sent for TB culture from 4 children). Conclusion: A definitive IGRA result is achievable in otherwise healthy children with close liaison between clinical and microbiology staff, prompt transfer of blood samples and incubating QFT-GIT samples within 4 hours of collection.

Evaluation of QuantiFERON-TB Gold Assay in detecting latent and active tuberculosis in group of Egyptian children
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Background: QuantiFERON-TB Gold In-Tube (QFG-IT) showed good diagnostic accuracy for active and latent TB in adults; limited studies have been performed regarding their use in children (DST) consists of two MTB-specific antigens - ESAT-6 and CFP-10 (tinkstaffink).

Methods: In a hospital-based prospective study, diagnostic accuracy of the tuberculin skin testing (TST) and QFT-IT were assessed in a cohort of 112 children (mean age 6.9±4.4, range 0.7-16), control not exposed (n=20), latent tuberculosis (n=44), active tuberculosis (n=50).

Results: In confirmed active TB, TST was positive in 24 out of 26 cases (92.3%), compared to 37 out of 50 cases (74%) for QFT-IT. None of the 2 tests performed significantly better than the other (p=0.109). In latent TB infection (LTBI), TST was positive in 24 out of 26 cases (92.3%), compared to 37 out of 50 cases (74%) for QFT-IT. Despite that QFT-IT performed better than TST, this was not statistically significant (p=0.062). Significantly higher number of positive QFT-IT and TST were seen in children older than 5 years compared to younger children (p=0.009, and 0.007, consecutively). The 2 tests did not show significant differences between those who had confirmed pulmonary and extra-pulmonary TB (p=0.05).

The overall agreement between the 2 tests was good (84.21%, k=0.677).

Conclusions: QTF-IT did not show higher diagnostic value in confirmed active childhood TB. Both QFT-IT and TST perform better in children older than 5 years than in younger population. Positive QFT-IT supports the diagnosis of TB in TST positive children. Negative QFT-IT does not exclude active TB. If used in diagnosis of LTBI, QFG-IT could significantly reduce the numbers of children receiving chemoprophylaxis.

Diagnostics of the latent TBC infection (LTBI) activity in children
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Material and methods: Under observation there were 118 children with LTBI and 129 diseased children with local forms of lung tuberculosis. The concentra-

tion of key cytokines IFN, IL4, IL10, IL18 in blood serum was identified with immunofluorometric method.

Results: To comparatively study the correlation of functioning of Th1 and Th2 cells in the immune response, we introduced the notion of “Cytokine index”. According to the secretory activity of T-helpers of the 1 and 2 type we determined by quantitative correlation of the key cytokines IFN/IL4 and IL10/IL18. It was determined that in comparison with a control group (30 noninfectious children) average values of IFN content increased in diseased children in 2,4 times, in lymphohy with LTBI – in 3,6 times. By analogy, the values of IL10 increased in diseased in 2,9 and in healthy children with LTBI – in 4,5 times. The obtained results underline the one-way direction of the immune response to TBC infection, appeared in organism. In diseased children the quantitative index of correlation of the key cytokines IFN/IL4 and IL10/IL18 was equal to 1,9. In healthy children with LTBI the this index was equal to 1,9. The correlation of the other two nonetheless important cytokines IL18/IL10 in the differentiating of T-lymphocytes in very indicative: in both groups the cytokine index appeared to be lowered to 1,4 and 1,9, which was caused by the increase of IL10 almost in 5 times compared with the control group (2,3).

Conclusion: The IL18/IL10 obtained results allow of IL18/IL10 introducing into clinical practice quantitative evaluation of correlation of Th1 and Th2 hence to diagnose the LTBI progress.

Tuberculosis detection in children and adolescents using diagnostic testing based on tuberculosis recombinant protein E SAGA-CFP10 (tinkstaffink)
Ludmila Slogotskaya1, Elena Ovsyankina1, Vitaly Livinovsky1, Yakov Kochetkov2, Petr Seltsovskiy2, O. Senchukina2, L. Stukheeva2, Dmitry Koudlay2, 1Clinical Research, Scientific and Clinical Anti-Tuberculosis Center, Moscow, Russian Federation; 2Research, Pharmacutamdont, Moscow, Russian Federation

Background: Until recently, the tuberculin skin test (TST) has been the only diagnostic method for latent tuberculosis infection (LTBI). However, the speci-
ficity of TST is low, because the purified protein derivative (PPD) used for TST contains numerous M. tuberculosis (MTB) antigens that are almost identical to BCG antigens or similar to non-TB mycobacterium (NTM) antigens. Of those 99% BCG vaccinated in Russia it is very difficult to diagnose LTBI. DIASIKTEST (DST) consists of two MTB-specific antigens - ESAT-6 and CFP-10, which are absent in all M. bovis BCG substrains and in most of NTM antigens. Aim was to evaluate to evaluate the role of DST in TB detection.

Method: 1675 children and adolescents with convurbed tuberculosis reaction, reaction size increased by more than 6 mm, hyperergy, TB contacts (social or household) received the Mantoux test with 2 TU PPD-L and DST 0.2 mg/kq/0.1ml.

Result: 95.8% - TST-positive. 349 (20.8%) - DST positive, all - chest X-ray plus computer tomography (CT). TB was diagnosed in 148 (42.4%). Out of them 6 were initially DST negative but after 3 months DST was repeated and resulted positive- active TB was diagnosed. In 19 (5.5%) TB was in the calcification phase. 9 TB contacts with established TB were DST-negative. All had BCG vaccination. 4 children one year old, probably, had not developed immunity. Two had contacts with TB/HIV parents.

Conclusion: DST allows detecting TB in 42.4% of cases. DST negative reaction could be in early aged TB patients – when immune response has not been developed yet. DST positive reaction may develop later in vaccinated children.
514. Integrated care and telehealth in primary care

P4984
Diagnostic value of non-specific humoral immune changes in children investigated for tuberculosis by skin test and bacteriology
Marina Spani1, Carmen Monica Pop2, Carmen Dana Sandru1, Daniel Cadar3, Mihaela Niculae1, Pompei Bolfa1,2, Infectious Diseases, USAMV, Faculty of Veterinary Medicine, Cluj-Napoca, Cluj, Romania; 1Pathology, USAMV, Faculty of Veterinary Medicine, Cluj-Napoca, Cluj, Romania.

It was suggested that repeated skin tests (IDR) used to diagnose childhood tuberculosis (TB) potentially change the immune response of the host. Adaptive cell-mediated immunity is the most important in protection against TB, but there is no information on the changes in the dynamics of immune globulins (Ig) and circulating immune complexes (CIC) in these patients. We hypothesized that the changes would be dependent on both the skin test results and bacteriological (BK) category of the subjects. The study was carried out in three groups of children, 1 to 17 years old, positive to both skin test and bacteriology (IDR+BK+, n=18), positive to the skin test but negative for bacteriology (IDR+BK-, n=12) and negative to skin test, but positive for bacteriology (IDR-BK+, n=9). Serum samples were subjected to total immunoglobulin (Ig) and immune complexes measurements (CIC), carried out by 0.24% zinc sulphate and 4.2% polyethylene glycol precipitation tests, respectively. Optical densities (optical density units, ODU) were red spectrophotometrically. The statistical significance of the results was estimated by Student’s t test.

Table 1-Total Ig and CIC levels of children tested for tuberculosis

<table>
<thead>
<tr>
<th>ODU</th>
<th>IDR+BK+</th>
<th>IDR+BK-</th>
<th>IDR-BK+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ig</td>
<td>0.40±0.126</td>
<td>0.37±0.099</td>
<td>0.58±0.141*</td>
</tr>
<tr>
<td>CIC</td>
<td>0.014±0.013</td>
<td>0.014±0.004</td>
<td>0.02±0.009*</td>
</tr>
</tbody>
</table>

*p<0.05.

The highest concentrations of immune globulins and circulating immune complexes, statistically significantly different (p<0.05), found in the IDR+BK+ group indicated the dependence of humoral changes on the presence of bacteria, rather than related to IDR, suggesting an added diagnostic value by use of these non-specific serological tests.

P4985
Electronic patient record as a facilitator to guideline based asthma management
Jean Holohan, Louis Coyne, Francis Guiney, Pat Manning, Basil Elhaziri, Eamonn Shanahan, Terry O’Connor, Muireann Ni Chroinin, Nettia Williams, Rhonda Forsythe, Pamela Logan. Research and Education, Asthma Society of Ireland, Dublin, Ireland; Respiratory, HSE Regional Hospital Mullingar, Mullingar, Ireland; Paediatric Respiratory/General Medicine, Adelaide and Meath National Children’s Hospital, Tallaght, Dublin, Ireland; General Practice, Farranfore Medical Centre, Farranfore, Killarney, Ireland; Respiratory, Mercy University Hospital, Grenville Place, Cork, Ireland; Paediatric Respiratory, Cork University Hospital, Wilton, Cork, Ireland; Professional Development Coordinator for Practice Nursing, Health Service Executive Dublin North East, Swords, Ireland; Director of Pharmacy Services, Irish Pharmacy Union, Dublin, Ireland.

Prior to the initiation of this project there was no consistent guideline based approach to an asthma consultation in primary care in Ireland. There is a lack of practice management systems but no consistent asthma module leading to variations in asthma management.

The Asthma Society of Ireland (ASI) collaborated with the Irish College of General Practitioners (ICGP) to develop locally modified GINA Guidelines as an initial step to developing an asthma specific Electronic Patient Record (EPR). The EPR was tested in 25 primary care sites; attitudes towards the EPR were evaluated using a 5 point Likert Scale.

The EPR captured demographic data, guided the consultation along a guideline based pathway through diagnosis, lung function tests, evaluation of asthma control according to GINA status, recorded medication and flu vaccinations, aided treatment selection in a step by step approach, identified patient educational priorities and objectives for next consultation. Data could be extracted to form a standardised referral letter to A&E or consultant. It provided a platform to develop personal action plans for the patient. Healthcare professionals (HCP) found the EPR easy to use (65%); EPR aids diagnosis (68%), assessment (90%), treatment selection (82.5%), and monitoring control (80%), facilitates patient education (85%) and helps with development of personal action plans (65%). HCP in primary care agreed that an asthma specific EPR facilitates guideline based asthma management. This EPR will provide the template for an asthma module in practice management systems in Ireland and ASI has engaged with stakeholders on the module development.

P4986
Perspectives of patients and healthcare professionals on the impact of telemedicine on hospital admissions for chronic obstructive pulmonary disease (COPD): A nested qualitative study
Peter Farbrook1,2, Hilary Pinnock1,3, Janet Hanley2, Lucy McCloughan1, Allison Todd1, Brian Mc Kinstry1, Centre for Population Health Sciences - GP Section, Medical School, University of Edinburgh, Edinburgh, United Kingdom; 2Centre for Integrated Healthcare Research, School of Nursing, Midwifery, and Social Care, Edinburgh Napier University, Edinburgh, United Kingdom.

Background: Early identification of exacerbations in COPD reduces hospital admission and may slow disease progression. There is increasing interest in telemedicine to support timely self-management of exacerbations. The TELE-SCOT randomised control trial based in Lothian, Scotland, is investigating the impact of a tele-monitoring service for COPD.

Aims: To explore the views of patients and professionals participating in the trial about the impact of telemetry on hospital admissions.

Method: We undertook semi structured interviews with patient and professional participants at different time points in the TELESCOT COPD trial. Transcribed, coded data was analysed thematically. Interpretation was supported by multidisciplinary discussion.

Findings: 38 patients (47% male, mean age 67.5 years) and 32 professionals provided 70 interviews. Both patients and professionals considered that home tele-monitoring reduced the risk of hospital admission. Patients used teledata to determine their state of health and to validate their decision to contact healthcare professionals earlier in order to prevent admission. Professionals emphasised the role of telemetry in encouraging compliance and facilitating patient self-management as a means of reducing admissions, though they also expressed concern that telememonitoring may increase patient dependence on services. The impact on the cost of services was a concern.

Conclusions: Enthusiasm for tele-monitoring as a means of reducing admissions is tempered by concerns about increased demand on support services.

Funding: Chief Scientists Office, Scottish Government.

P4987
The effect of integrated care on asthma control
Maarten Prinsen1, Ellen Van Heijst1, Sigrid Schokker1, Corina de Jong1, Roland Riemsma1, Jan Willem Kocks1, Thys van der Molen1, Department of General Practice, University Medical Center Groningen, Groningen, Netherlands; 2Asthma and COPD Service, Luhbeurt, Groningen, Netherlands; 3Groningen Research Institute for Asthma and COPD, University Medical Center Groningen, Groningen, Netherlands.

Background: Integrated care of respiratory patients has often been advocated, however, the effect on patient outcome is not clear.

Objective: To describe the effect of an integrated care system on asthma control.

Method: We developed an integrated care system for communication between pulmonologists and General Practitioners (GP). In this system patients with res-
piratory problems complete questionnaires (history, control and health status) and visit the laboratory for spirometry. These data are collected and uploaded to a central server. Based on these data without seeing the patient and supported by a decision support system (DSS), pulmonologists (n=9) give advice about diagnosis and treatment to the GP (n=250), who treats the patient.

Results: From a total of 7877 patients referred to our integrated care system 3721 patients were diagnosed with asthma. In 889 of these patients ACQ data were available at baseline and follow up. The median ACQ scores at baseline (1.0) proved to be significantly different from the median ACQ scores of the follow up visit (0.7) (Z= -8.81, p <0.001). Improvement of asthma control ≥ MCID (0.4) was measured in 32% of patients (n=284). Additionally the results showed deteriorated asthma control in 15% of patients (n=134) and unchanging asthma control in 51% of patients (n=454).

Table 1. Amount of patients per ACQ cut-off value per visit

<table>
<thead>
<tr>
<th>ACQ Cut-Off</th>
<th>Baseline</th>
<th>Second visit</th>
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</thead>
<tbody>
<tr>
<td>&lt;0.75 Stable</td>
<td>Frequency</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>42</td>
</tr>
<tr>
<td>0.75–1.50</td>
<td>Frequency</td>
<td>251</td>
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<tr>
<td></td>
<td>Percent</td>
<td>28.2</td>
</tr>
<tr>
<td>&gt;1.5 Unstable</td>
<td>Frequency</td>
<td>265</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>29.8</td>
</tr>
</tbody>
</table>

Patients grouped per ACQ cut-off per visit.

Conclusions: This integrated care model improved asthma control.

P4998

Teleconsult-pro technology in the Netherlands

Christian F. Melisant1, Joep Hoevenaars 2. 1Pulmonology, Spaarne Hospital, Hoofddorp, Netherlands; 2Telemedical Centre, Kuyos, Amstelveen, Netherlands

Diagnosing obstructive pulmonary disease has proven difficult in primary practise, leading to incorrect referrals. In teleconsult-pro technology general practitioners (GPs) digitally consult pulmonologists for advice on spirometry. We hypothesized, that teleconsult-pro technology, applied after patient selection by the GP, would reduce referrals and improve triage of referrals.

GPs log on to a secured web-based teleconsultation system (KSYOS) and send a lung function (PDF) and - voluntarily - some clinical information to the pul monologist. Its purpose was to ask advice or to prevent referral. 293 closed teleconsultations were analyzed.

The GP answers two quality indicators, before (Q1) and after (Q2) each teleconsultation:

(Q1): Without teleconsultation, would you have referred this patient to the hospital? (Q2): Will you refer this patient to the hospital?

Quality indicator results

| Q2 = yes | 26 | 75 | 101 |
| Q2 = no  | 42 | 150 | 192 |
| Total    | 68 | 225 | 293 |

Of the total 101 teleconsultations intended for referral, 75 referrals (74%) were pre- vented. Of 192 teleconsultations intended for advice (2/3 of all teleconsultations), 42 patients (22%) were referred after teleconsultation. Although still small numbers, this analysis shows a reduction in referrals to the pulmonologist, which in times of necessary cost-reduction is very interesting and helpful for insurance companies. Furthermore, teleconsultations showed initially unforeseen referrals, consisting of patients having a pulmonary disease, who needed to be investigated more properly in hospital.

P4999

RECODE: RCT on effectiveness of integrated COPD management in primary care

Annemarie Jruis1, Melinde Roland2, Pin Assendelft1, Jacobijn Gussekloo1, Apostolos Tsichrista1, Maureen Rutten2, Jaap Sont3, Niel Chavannes1

1Public Health and Primary Care, Leiden University Medical Centre, Leiden, Netherlands; 2Institute for Medical Technology Assessment, Erasmus University, Rotterdam, Netherlands; 3Medical Decision Making, Leiden University Medical Centre, Leiden, Netherlands.

Background: There is insufficient evidence of the (cost)effectiveness of primary care COPD disease management programmes. Aim and objective: To evaluate the (cost)effectiveness of an ICT-supported, in- tegrated, multidisciplinary disease management program for primary care COPD patients. We expect health care providers to improve inter-collegial communica tion, personalized treatment planning and better adherence to guidelines. As a result, we expect quality of care and quality of life in patients to improve.

Methods: The study has a two-group cluster-randomized design in which 40 clusters of primary care teams are being randomized. Required sample size is 1080 COPD patients, in accordance with GOLD. Few exclusion criteria are applied. The intervention consists of a multidisciplinary course (2 days) in which primary care givers (general practitioners, practice nurses, phytotherapists, dieticians) within a particular region are trained as a team. The course will emphasize efficient task delegation within the team, active patient involvement in treatment planning, and designing time-contingent practice plans. Primary outcome is difference in health status as measured by Clinical COPD Questionnaire (CCQ). Programme, costs, vertical and horizontal integration utilisation and productivity loss will also be calculated. Primary endpoint is at 12 months, while total study duration is two years.

Results: Until now 496 patients have been included, which preliminary baseline were means of FEV1/FVC ratio 56%, FEV1 65% predicted, CCQ score 1.65, MRC score 2 and EQ-5D score 0.71.

Conclusion: The RECODE study is a cluster randomized trial which will provide insight in the cost-effectiveness of this particular primary care COPD disease management programme.

P4991

Diagnosing COPD and asthma in primary care in Israel – The challenge and the change

Eitan Brodsky, Sigal Ringel, Meir Raz. Jerusalem and Shfela District, Maccabi Healthcare Services, Tel Aviv, Israel

Background: Under-diagnosis and misdiagnosis of COPD and Asthma leads to inadequate treatment and incorrect use of healthcare resources. Maccabi Healthcare Services, one of the leading HMOs in Israel, has decided to promote the correct diagnosis by the primary physician and to establish a computerized patient register based on validated diagnoses.

Objectives: 1. To increase the ability of diagnosing COPD and Asthma at the primary care level. 2. To validate the currently exist diagnoses that in the medical files. 3. Diagnostic standardization and later - treating these diseases according to the standard clinical guidelines.

Methods: 1. Developing the ability to conduct spirometry in Maccabi clinics, according to the referral of primary physicians or Allergy or Pulmonology specialists. 2. Developing a flow process to interpret and report spirometry results to the patient's central medical records by Pulmonology specialists. 3. Establishing a computerized register of COPD and Asthma patients. 4. Training among designated technicians and increasing knowledge and awareness among primary physicians regarding validated diagnosis of lung diseases.

Results: Since the inception of the service at the end of 2009, spirometry devices were placed in 13 primary care clinics in the Jerusalem and Shfela region, approx. 2200 patients underwent a spirometry examination, and an computerized register based on validated diagnoses is currently being completed.

Conclusions: Early diagnosis among high-risk populations will promote appropriate treatment. Validation of the diagnoses will enable the system to properly deal with the more accurate level of the rising morbidity of COPD and Asthma.

P4992

Successful implementation of asthma guidelines in Thailand: The Easy Asthma Clinic model

Wachara Boonsawat. Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand

Introduction: Asthma management guidelines were published in Thailand in 1994 and revised in 1997 following the publication of the GINA guidelines. However, the audit made by the National Health Security Office (NHSO) showed that asthma management in Thailand fell short of the goals determined for long-term asthma care indicated the failure of guidelines implementation.

Method: We have developed Easy Asthma Clinic Network as a model to enhance the implementation of GINA guidelines in Thailand since 2004. Easy Asthma Clinic runs by GPs in general hospitals. In the clinic we simplified asthma guidelines and organized the system to facilitate the team work, emphasized the role of nurses and pharmacists to help doctors. We also developed on-line web database for registering and monitoring patients. In 2009 NHSO support the set up of Easy Asthma Clinic in all hospitals in Thailand.

Results: Easy Asthma Clinic was set up in more than 900 hospitals in Thailand. 99,535 asthmatics were registered with 548,583 visits. Easy asthma clinics improve quality of asthma care in general hospitals. Peak flow measurement were improved from 1.08% to 98.47% of the visits. Inhaled corticosteroids used increased 10.92% to 79.30%. Asthma controlled were achieved in 23.19% of visits and partly controlled in 46.35%. Conclusions: Setting up Easy Asthma Clinic help implementation of asthma guidelines in Thailand.

P4993

The effect of integrated care on health status in COPD

Maarten Prinsen1, Ellen Van Heijst2, Siebrig Schokker1, Corina de Jong1, Roland Riemersma1, Jan Willem Kocks1, Thys van der Molen1. 1Department of General Practice, UMC Groningen, Groningen, Netherlands; 2Asthma and COPD Service, LAbvloed, Groningen, Netherlands; 3Groningen Research Institute for Asthma and COPD, UMC Groningen, Groningen, Netherlands.

Background: Integrated care of respiratory patients has often been advocated. However, the effect on outcome in COPD patients is unclear.

1Department of General Practice, UMC Groningen, Groningen, Netherlands; 2Asthma and COPD Service, LAbvloed, Groningen, Netherlands; 3Groningen Research Institute for Asthma and COPD, UMC Groningen, Groningen, Netherlands.
**Wednesday, September 28th 2011**

**Objectives:** To describe the effect of advice from an integrated care system on health status in COPD patients.

**Method:** We developed an integrated care system in which pulmonologists provide diagnostic support to the General Practitioner (GP). Patients with respiratory problems complete questionnaires (history, control and Clinical COPD Questionnaire (CCQ)) and visit the laboratory for sputometry. These data are collected and uploaded to a central server. Based on these data without seeing the patient and supported by a decision support system the pulmonologist (n=80) give advice about diagnosis and treatment to the GP (n=250) who treats the patient.

**Results:** From 7877 patients referred to the integrated care system, 1331 patients were diagnosed with COPD. In 310 of these patients CCQ data were available both at baseline and follow up (3 months or 1 year). The median CCQ score of the baseline visit (1.1) proved to be significantly different from the median CCQ scores on the second visit (1.0) (Z = -2.48, p=0.013). Improvement of health status ≥ the minimal clinical important difference (MCID) of 0.4 was measured in 27% of patients (n=82). Deteriorated health status ≥ the MCID was reported by 29% of patients (n=85). Patients reported unchanging health status (n=135).

**Discussion:** This integrated care model where the pulmonologist directly advises the GP provided an overall statistical significant improvement of COPD health status. Clinical implications however are unclear.

**P4994**

Healthcare professional attitudes towards asthma guidelines in primary care

Jean Holohan, Louis Coyne, Francis Guiney, Pat Manning, Basil Elmagir, Eamonn Shanahan, Terry O’Connor, Muireann Ni Chronin, Nette Williams, Rhonda Foy, Pamela Logan, Research and Development, Asthma Society of Ireland, Dublin, Ireland; Respiratory, HSE Regional Hospital Mullingar, Mullingar, Ireland; Pneumatic Respiratory/General Medicine, Adelaide and Meath National Children's Hospital, Tallaght, Dublin, Ireland; General Practice, Farranfore Medical Centre, Farranfore, Killarney, Ireland; Respiratory, Mercy University Hospital, Grenville Place, Cork, Ireland; Pneumatic Respiratory, Cork University Hospital, Wilton, Cork, Ireland; Professional Development, Coordinator for Practice Nursing, Health Service Executive Dublin North East, Swords, Dublin, Ireland; Director of Pharmacy Services, Irish Pharmacy Union, Dublin, Ireland

Implementation of guidelines in primary care can be challenging but are essential to reduce the burden of asthma for patients and health service providers and to reduce hospital admissions and mortality and to deliver cost effective care.

The Asthma Society of Ireland (ASI) in conjunction with the Irish College of General Practitioners (ICGP) locally adapted the GINA Guidelines as a first step to providing guidelines based asthma management in primary care. The ASI funded and developed a guideline based program to evaluate healthcare professional (HCP) attitudes to these guidelines and ensure user buy in prior to national implementation.

25 primary care teams participated in the program. The HCP completed guideline based education and practical training. Patients were recruited to follow the asthma management program for 6 months. HCP were asked to evaluate both educational and training components and practical resources provided for the program. Attitudes towards guideline implementation were evaluated using a 5 point Likert Scale.

Final analysis of HCP survey in response to the locally modified guideline (89% response rate) showed guidelines were easy to follow (92.7%), helped with decision making (92.6%), improved the clinical decision making process (70.8%), improved patient care (92.7%), reduced inappropriate variation in management (77.5%), facilitated cost effective care (70.7%).

HCP in primary care agreed that guideline based management is an integral component to the implementation of best practice asthma management. The Irish Health Service Executive has incorporated the locally modified guideline and associated asthma education program into the core components of the new National Asthma Program.

**P4995**

Clinical decision support system for diagnosing patients with community-acquired pneumonia

Shigeto Hanada1, Hitonori Uruga1, Hiashi Takaya1, Atsushi Miyamoto1, Hideyasu Sugimoto1, Nasa Morokava1, Atuko Kurosaki2, Kazuma Kishi1, Shouji Kanada1, Akira Osawa1, 1Department of Respiratory Medicine, Toranomon Hospital, Minato-ku, Tokyo, Japan; 2Department of Diagnostic Radiology, Toranomon Hospital, Minato-ku, Tokyo, Japan; 3IT System Development Center, Medical Development Group, Fuji Photo Film, Minato-ku, Tokyo, Japan

**Objective:** To examine whether a Clinical Decision Support System (CDSS) is specific enough to reliably predict the etiology of community-acquired pneumonia (CAP).

**Methods:** We developed an application program named CDSS comprising of information relating to epidemiologic conditions, risk factors, clinical manifestations, and laboratory findings of 53 patients with CAP who were seen at Toranomon Hospital from April 2006 to April 2010. We also studied other 17 CAP patients with definitive etiologies and collected information required for calculating similarity. The best matches among the cases in CDSS were returned in a list, and sorted by similarity score, with the most similar one presented first. We assessed the usefulness of CDSS in differentiating etiologies of patients with CAP.

**Results:** There were 11 men and 6 women with a mean age of 59 years (range: 26–86). The etiologies of CAP were Streptococcus pneumoniae in 4 patients, Mycoplasma pneumoniae in 3, Haemophilus influenzae in 2, aspiration pneumonia in 2, Mycobacterium tuberculosis in 2, Nontuberculous mycobacterium in 2, Pseudomonas aeruginosa in 1, and diffuse panbronchiolitis in 1, respectively. Based on the results of CDSS, we identified the correct diagnosis with the highest similarity in 8 of 17 patients (47.1%). Differentiation between bacterial pneumonia and atypical pneumonia could be made in 10 of 12 patients (83.3%). The four cases of Mycobacterium tuberculosis and Nontuberculous mycobacterium could be easily be differentiated from other pathogens (100%).

**Conclusion:** CDSS is a new approach that can be used by clinicians to predict the etiology of CAP.

**P4996**

Asthma self management preferences, attitudes and beliefs in primary care

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**Purpose:** To describe self management preferences, attitudes and beliefs of urban adults with persistent asthma.

**Subjects:** Primary care patients prescribed inhaled corticosteroids (ICS).

**Methods:** Survey

**Results:** A convenience sample of 141 subjects (78% female; 81% Black; 51% with ≤ high school education; 29% with commercial insurance; mean age 50.4 ± 13.4; range 19-83) prescribed inhaled ICS for persistent asthma were enrolled from 5 sites (2 internal medicine, 2 family medicine, 1 pulmonology + internal medicine). One hundred and thirty-nine (92%) of the patients completed the survey. No differences were found among subjects who completed the survey vs non-responders. The most common reasons for using ICS were to reduce the number of symptoms and side effects (93%), reduce exacerbations (85%), maintain asthma control (89%), help the physician with their care (83%) and cost effectiveness (81%). On a 5 point Likert scale, the subjects rated the most important reasons for using ICS were to reduce the number of symptoms and side effects (88.1%), maintain asthma control (83.7%) and cost effectiveness (82.7%).

**Conclusion:** Patients have unique self management preferences, attitudes and beliefs that, if identified and discussed, could serve as the foundation of a tailored plan of care that may reduce barriers to ICS use.

**P4997**

Improving asthma control with therapeutic education intervention

Lalita Fernandes, Anthony Mesquita. TB and Respiratory Medicine, Goa Medical College, S. Inez, Caranzalem, Goa, India

**Objective:** To assess the level of control in asthma patients receiving therapeutic education intervention.

**Background and significance:** There is no cure for asthma, hence the aim of management is to control asthma and improve quality of life. One of the reasons for poor control is improper inhaler technique. We analysed the control of asthma in subjects who received inhaler technique education by trained respiratory therapists.

**Methods:** In a randomised controlled trial, we enrolled 89 new uncontrolled non-smoking asthma patients reporting to the hospital. Asthma was confirmed by symptoms and spirometric reversibility as per ATS/ERS 2005 standards. Patients with asthma exacerbation and requiring systemic steroids were excluded. All 89 patients were treated with appropriate medications and were then randomised to education intervention group (teaching of correct inhaler technique by respiratory therapist) and the control group received routine inhaler technique instructions by the physician. Both groups were followed up at 4 weeks. The intervention group was reassessed for inhaler technique at 4 weeks. At 12 weeks both groups were assessed for asthma control using ACT.

**Results:** There was significant improvement in asthma control in the group.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>Age(SD)</td>
<td>41(14)</td>
<td>41(12)</td>
</tr>
<tr>
<td>Sex</td>
<td>32 (74%)</td>
<td>31 (67%)</td>
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<tr>
<td>Females</td>
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</table>

Chi square=7.083, df=1, p=0.008.
P4998 Caregiver perception versus patient reality: A Canadian perspective on COPD

Donna Goodridge1,2, Shelly Hutchinson1, Darcy Marciniuk1, Donna Rennie3.
1College of Nursing, University of Saskatchewan, Saskatoon, SK, Canada; 2Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada; 3College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

Background: The high health care utilization of many patients with advanced COPD may reflect sub-optimal preparation of the patient and caregiver to effectively manage COPD upon discharge. Purpose: To examine the care transition experiences of COPD patients and their caregivers regarding care transition quality within two weeks of discharge from hospital.

Design: This cross-sectional study included 22 dyads (N=44) of patients with advanced COPD (MRC 3, 4 or 5) and their caregivers in two Canadian cities. The Care Transitions Measure (CTM-15) was used to obtain scores from both the patients and caregiver on the quality of care transition. CTM-15 scores range from 0-100, with higher scores indicating higher quality of care transition. Correlations between CTM-15 scores, global rating of health and the Clinical COPD Questionnaire (CCQ) were assessed.

Results: Median CTM-15 score for patients was 58.9 (IQR=30.5) compared with 46.7 (IQR=16.5) for caregivers (NS). The majority of participants (78.6%) had clear health goals upon discharge (63.6%) a written plan of care (59.1%). Caregivers did not understand warning signs and symptoms to monitor (72.7%), understand how to manage the patient’s health (68.2%) or have all the information needed to be able to take care of the patient upon discharge (54.5%). CTM-15 scores were negatively correlated with CCQ scores (r=-0.04) but not with global rating of health.

Interpretation: COPD patients and their caregivers require additional preparation for discharge and reported important gaps that have important implications for self-care in the community. CTM-15 scores in this study were lower than those previously reported in geriatric literature.

P4999 COPD patient and caregiver assessments of care transition quality

Donna Goodridge1, Shelly Hutchinson1, Darcy Marciniuk1, Donna Rennie3.
1College of Nursing, University of Saskatchewan, Saskatoon, SK, Canada; 2Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada; 3College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

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Interpretation: COPD patients and their caregivers require additional preparation for discharge and reported important gaps that have important implications for self-care in the community. CTM-15 scores in this study were lower than those previously reported in geriatric literature.

P5000 Time course of diaphragm function recovery after mechanical ventilation in an animal model

Debby Thomas, Karen Maes, Anouk Agetn, Marc Decramer, Ghislaine Gayan-Ramirez. Laboratory of Pneumology, KU Leuven, Leuven, Belgium

Rationale: Several studies have previously shown that controlled mechanical ventilation (CMV) results in rapid and severe diaphragmatic dysfunction. On the other hand, the recovery response of the diaphragm to normal function after mechanical ventilation is not known, although these data may have an impact on weaning from the ventilator. Therefore we examined the time-course of diaphragm function recovery in an animal model of CMV.

Methods: Rats were anesthetized and submitted to 24-27h of CMV or 24h of CMV followed by either 1h, 2h or 3h of spontaneous breathing (CMV + 1h SB, CMV + 2h SB, and CMV + 3h SB, respectively).

Results: There were no differences in blood pressure, blood gases, body weight or muscle weights between the four groups. The in vitro diaphragm force-frequency curve was similar in the CMV, CMV + 1h SB and CMV + 2h SB groups. Three hours of SB after CMV resulted in a significant improvement of diaphragm force compared to the other groups (eg, maximal tetanic force: ±29% vs CMV, p<0.01).

Diaphragm cross sectional area (CSA) of the type I and type Ila fibers was similar in all groups, while the CSA of the type IIX/b fibers was significant increased in the CMV + 3h SB group (16.7% vs CMV, p<0.05). No differences were observed in the activity of the proteolytic enzymes calpain and caspase-3. Protein oxidation was similar in the diaphragm in all groups.

Conclusions: These data show that, in rats, relading the diaphragm for 3h after CMV is sufficient to result in significant improvement of the diaphragm force together with an increase in the CSA of the type IIX/b muscle fibers. Funded by: FWO-Flanders G.0893.11 and AstraZeneca Pharmaceuticals

P5001 Mechanical ventilation induces a time-dependent reduction in diaphragmatic blood flow

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Introduction: Continuous mandatory ventilation (CMV) induces atrophy of the diaphragm, contributing to ventilator induced diaphragmatic dysfunction (VIDD), which is significant after 6 h of CMV. However, the effects of prolonged CMV on diaphragmatic blood flow remain unknown. Therefore, we tested the hypothesis that long term CMV (6 h) will further decrease diaphragm perfusion versus that measured during acute CMV (30 min) and may contribute, in part, to VIDD due to reduced oxygen delivery.

Methods: Blood flow to the diaphragm and other skeletal muscle was assessed (via the radioactive microsphere technique) during spontaneous breathing (SB) and after 30 min and 6 h of CMV in female Sprague-Dawley rats (n=42). Blood pressure and heart rate were monitored continuously throughout the protocol.

Results: In the midcostal portion of the diaphragm blood flow decreased by ~22% from SB to 30 min CMV, with a further reduction in flow of ~37% after 6 h CMV (i.e., SB 28.3±3.5 vs. CMV, 30 min 19.3±2.9; 6 h 8.8±0.6 ml/100 g/min; P<0.05). The other constituents of the diaphragm demonstrated a similar trend in perfusion over time. Blood flow to other hindlimb skeletal muscle did not decrease significantly at any time point.

Discussion: Our study demonstrates, for the first time, that there is a time-dependent reduction in diaphragmatic perfusion during prolonged CMV. Further, a decrease in blood flow over the same time period was not observed in other skeletal muscles, even with matched oxidative capacities (e.g., red. portion of the gastrocnemius). Our data indicate that prolonged CMV elicits vascular dysfunction in the diaphragm which may contribute, in part, to the ongoing process of VIDD.

P5002 High dose methylprednisolone counteracts the negative effect of rocuronium on diaphragm function in a rat model of mechanical ventilation

Karen Maes, Dries Testelmans, Debby Thomas, Marc Decramer.
Ghislaine Gayan-Ramirez. Laboratory of Pneumology, KU Leuven, Leuven, Belgium

Rationale: We previously showed that rocuronium (ROC) combined with 24h of controlled mechanical ventilation leads to an additional negative effect on diaphragm function in rats. Based on clinical observations we hypothesized that the combination of rocuronium with corticosteroids in our animal model of CMV would result into a further deterioration of diaphragm function.

Methods: Mechanically ventilated (24h) rats received intravenously either a con-

515. Mechanical ventilation and weaning

PG008

PG009
Abstract P5005 – Table 1

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<td>Lactate (mmol/L)</td>
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<td>K+ (mmol/L)</td>
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<td>Anion Gap</td>
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<tr>
<td>Normal range</td>
<td>7.35–7.45</td>
<td>4.6–6.0</td>
<td>22–26</td>
<td>0.7–2.1</td>
<td>3.3–4.5</td>
<td>8.0–12.0</td>
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<tr>
<td>Mean ± SD</td>
<td>7.1±0.1</td>
<td>4.02±0.13</td>
<td>11.2±0.51</td>
<td>0.8±0.5</td>
<td>3.5±0.55</td>
<td>20.1±8.0</td>
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Results: A total of 100 patients on MV were included in the study. Ninety percent of patients were successfully weaned. Unsuccessfully weaned patients had higher PIV and were more likely to be maintained on RPV compared to the rest of the population.

Conclusion: In older DMD patients on iPAP we observed that severe, metabolic acidosis related to chronic constipation and its treatment, reduced fluid and food intake and associated respiratory infection resulted in a life-threatening condition.

Grant support: Lunge Zürich.

PS004

Predictors of successful weaning from mechanical ventilation

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Background: For adult patients on mechanical ventilation, successful weaning has been attributed to various factors. The purpose of this study was to describe patient outcomes, and factors in successful weaning.

Patients and methods: This study included 100 patients (45 males & 55 females) with mean age of 57.8 years, with respiratory failure due to different pulmonary diseases (bronchial asthma, COPD, IPF, pneumonia and malignancy) and were admitted to ICU for mechanical ventilation between October 2008 to October 2010.

Results: The additional negative effect of RPV on the diaphragm during weaning was evident from s1 to s4, unlike NA V A and PCV. In both steps, higher ETD and lower WOB due to patient-conditioned work of breathing (WPs).

Conclusion: In older DMD patients on iPAP we observed that severe, metabolic acidosis related to chronic constipation and its treatment, reduced fluid and food intake and associated respiratory infection resulted in a life-threatening condition.

Grant support: Lunge Zürich.

PS005

Neurally adjusted ventilatory assist (NAVA) in difficult-to wean patients

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Aim: To compare physiological effects of NAVA with Pressure Support Ventilation (PSV) and Pressure Controlled Ventilation (PCV) in difficult-to-wean patients on non-invasive ventilation.

Methods: Six tracheostomised awake WPs (2 males, age 68±28.8y) under prolonged (>13 days) mechanical ventilation (MV) underwent physiological evaluation during three 20 minute MV sessions, randomly applied, with NAVA, PSV and PCV. Airway pressure (Paw), airflow, and diaphragm electrical activity (EAdi) were derived from ventilator (Servo i, Maquet). Changes in tidal volume (Vt), inspiratory (ITD) and expiratory (ETD) time delay, and EAdi-related work of breathing (Dob) were used to assess weaning. The number of MV sessions was 6.

Results: In PSV, an increase in EAdipeak, WOB, and a decrease in Vt, Ve were observed from s1 to s4, unlike NAVA and PCV. In both steps, higher ETD and WOB in PCV compared to NAVA were found.

Conclusion: In WPs, NAVA was associated to reduced WOB due to patient-ventilator delay.

PS006

Predicting the outcome from noninvasive ventilation for acute exacerbation of chronic obstructive pulmonary disease in the emergency department

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Objectives: To identify early objective clinical parameters and biomarkers for severity assessment and predicting outcomes in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) requiring noninvasive mechanical ventilation (NIV).

Methods: Three-months observational prospective study in the acute setting of the ED of a university teaching hospital, including consecutive nonselected patients evenly admitted for ARF due to AECOPD treated by NIV according to EP's indication referring to an institutional protocol. Treatment failure was defined as hospital mortality or need for invasive mechanical ventilation at any time.

Results: 124 patients (media 1.38/day). Failure (23 cases, 18.5%) and success (101; 81.5%) patients were different in: neurologic status score (Kelly-Matthy scale), urea, creatinin, AST, ALT, CPK, CPK-MB, troponin T, LDH, PCR, pH, and arterial blood gas analysis parameters after 1 hour of NIV (PaO2, pH, PaCO2, HCO3–, SaO2, PaO2/FIO2).

Conclusion: NIV is a cost effective intervention even outside intensive care units for the treatment of ARF caused by AECOPD. We were able to identify in the early predictors of outcome (mainly about more severe clinical conditions and the
response to treatment). An unresolved question in the ED is about selection criteria and early choices for patients with ARF having preset therapeutic-prognostic limits and acutely reversible processes for which NIV should be considered as ceiling treatment.

P5007
Acute exacerbations of COPD (AECOPD) in intensive care unit (ICU): Are non-invasive ventilation (NIV) use and mortality different in high volume ICUs?
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Introduction: NIV for the management of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) increased last decades. ICU teams caring for a high number of AECOPD could gain more experience and therefore use NIV in a higher proportion of patients. The case-volume could also be associated with ICU mortality.

Material and methods: The French CUB-REA database includes 32 ICUs. AECOPD cases were extracted according to ICD-10 coding. To assess the effect of case volume on NIV use, invasive ventilation (IV) use and mortality, multivariate analysis using mixed models were performed to adjust for severity of illness and other concurrent factors.

Results: Between 1998 and 2008, 6,434 AECOPD were identified. SAPS II and ICU mortality gradually increased (35% to 41 and 1% to 16%, respectively). The proportion of patients receiving any mechanical ventilation increased (66% to 85%), with a marked increase in the use of IV (from 19% to 43%) and a decrease in the use of IV (35% to 23%). Case volume tertiles were: low volume (10 admissions per year), intermediate (10-26) and high volume (more than 26). There was a significant association between case volume, IV use and ICU mortality: OR for the highest versus lowest and intermediate tertiles were: 5.61 [95% CI: 0.73-0.94], respectively.

Conclusion: During this period, the severity and mortality rate of AECOPD admitted in CUB-REA ICUs increased. There was a growing use of NIV and a decreased use of IV. NIV use and ICU mortality were related to case volume, suggesting that increasing experience favours the use of NIV without impairing patients’ outcomes.

P5008
Low-t3 state a crucial biomarker in determining NIV failure and outcome in pulmonary patient?
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Background: Various low T3 states have been described in severe nonthyroidal diseases; they have been associated with a poor prognosis in cardiovascular and pulmonary disease patients. Aim: To investigate the role of T3 function in patients suffering from respiratory failure (RF), needing invasive or non-invasive mechanical ventilation (NIV), in order to evaluate the prognostic value of nonthyroidal illness syndrome in NIV failure.

Methods: We studied retrospectively 32 consecutive patients with acute or acute on chronic RF needing mechanical ventilation. Measured variables upon admission included: APACHE II score, the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired gas (PaO2/FiO2), plasma levels of freeT3 (fT3), freeT4 (fT4), and Thyroid Stimulating Hormone (TSH) levels.

Results: Plasma levels of fT3 were below normal range in 17 patients (53%). Plasma fT3 correlated with PaO2/FiO2 (p<0.001), and with APACHE II score (p=0.003). Ten patients with low levels of fT3 needed invasive mechanical ventilation due to NIV failure. These patients, with comparable APACHE II score and gas exchange, showed fT3 value significantly lower than patients improving with NIV. fT3 levels were significantly lower (p=0.002) in four patients (12.5%) who died, in comparison to the patients who survived. fT3 value was the only factor significantly associated with an increased risk of death, according univariate logistic regression analysis (Odds Ratio 64.23, 95% Confidence Interval 1.78 to 2316.86, p=0.023).

Conclusion: Our data suggest that low T3 state can predict NIV failure and outcome in pulmonary patients with acute RF.

P5009
Evaluation of adrenal function in patients receiving invasive and noninvasive mechanical ventilation
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Aim: Although adrenal insufficiency (AI) is a rarely seen condition in critically ill cases (2-3%), it is reported that relative AI is encountered more frequently. In this study, our aim was to detect the frequency of AI using standard dose corticotropin (ACTH) test in patients with critical illness and to determine IL-6, adrenalin, BAL cortisol, prolactinemia and 24-hour uriner cortisol values effects of the prognosis.

Material and method: A total of 80 patients with acute critical illness were recruited to the study. The patients were divided into two groups according to the applications of IV and NIV. Vital findings and APACHE II scoring were recorded and blood samples were taken for ACTH and cortisol. Furthermore, standard dose (250 μg) ACTH test was done for AI diagnosis.

Results: AI defined in patients according to the basal cortisol < 15 μg/dl and/or delta cortisol < 9 μg/dl. AI were determined in 18 patients (22.5%). AI was detected in 6 (15%) of the 40 patients who were received IV. Thirty two of these 40 patients died. AI was determined at 4 (12.5%) of these 32 patients who were died. There was AI in 12 (30%) of 40 patients to whom NIV was applied. 12 of these 40 patients died. Two (16.7%) of these 12 patients who died bad AI. In patients with and without AI, there was no significant difference with respect to the mortality rates at the IV and NIV group (p>0.05).

Conclusion: The frequency of AI was uncommon in patients with critical illness. AI was determined more frequently at the NIV group. We think that adrenal functions should be routinely followed in the intensive care even though there was no clinical finding.

P5010
A novel way of heliox administration in patients with COPD exacerbation
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Introduction: Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. The purpose of heliox (helium and oxygen mixture) administration in patients with severe COPD exacerbation is to avoid invasive ventilation which is recognized as an adverse prognostic factor.

Aims: The aim of the study is to test suitability of a modified semi-closed anesthetic circuit with CO2 absorber for heliox administration. The circuit may offer a safe way of heliox administration to spontaneously breathing patients at significantly reduced costs.

Methods: The semi-closed circuit was evaluated by work of breathing (WOB) measurement in healthy volunteers (N=9) who signed the informed consent. An endobronchial balloon catheter was used for carbon dioxide measurement. The resistive component of WOB and pressure-time product (PTP) were calculated; O2 consumption and end-tidal CO2 were evaluated. These parameters were compared with the corresponding parameters obtained during spontaneous ventilation on air.

Results: WOB was increased by 15% and PTP was increased by 12% during the spontaneous ventilation with heliox using the semi-closed circuit compared to the ventilation on air.

Conclusion: The study showed that administration of heliox using the semi-closed circuit increases WOB and PTP for a patient due to the intrinsic resistance of the circuit. Nevertheless, as resistance of the airways and WOB are increased during COPD exacerbation, the semi-closed circuit using the semi-closed circuit does not represent a significant workload for patients with COPD exacerbation.

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P5011
Sleep monitoring with portable devices in ICU patients
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Introduction: Sleep disruption and deprivation is a continuing problem in the Intensive Care Unit, but measures to improve sleep cannot utilize traditional polysomnography. Practical, non-intrusive diagnostic monitoring of sleep is required.

Aim: To 1) test two new portable ambulatory sleep diagnostic devices to monitor sleep in ICU and 2) compare sleep data generated by the different devices.

Methods: The devices were a) Wink/hPAT 200 (Illumar Medical), wrist watch-style, employing peripheral arterial tonometry and actigraphy to evaluate sleep time and sleep stage by an automatic algorithm (PAT device) and b) ALICE PDx (Respironics Philips), miniature polysomnographic device utilizing EEG and EMG recordings, with technician scoring (Mini-PxG device). Both include oximetry and position sensors. Seven ICU patients provided informed consent (mean age 68 years) and were recorded wearing both devices, from 21:00 to 06:00.

916s
Results: Both devices successfully monitored sleep in ICU patients. The PAT device was less intrusive with size and attachments. Saturation and heart rate oximetry data were identical from the devices. Both devices calculated total sleep time (TST), and detected changing sleep stage. There were significant differences in reported values. Mean TST reported was 365 and 507 min., for Mini-PAT and PAT device, respectively, difference 28%. Similarly, REM sleep time was 7.9 and 16.1%TST for the devices, difference 51%. There were large inter-patient variance; some patients showed similar results from both devices.

Conclusions: Portable sleep diagnostic devices can successfully monitor sleep in ICU patients. Devices based on different sensor recordings may generate different calculations of sleep time and stage.

P5012
Sleep quality in prolonged mechanical ventilation patients
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Intensive Care Unit (ICU) patients recovering from critical illness often present persistent respiratory failure and require prolonged mechanical ventilation (PMV). The aim of this study was to assess sleep quality in PMV patients, during hospitalisation in ICU and in a Respiratory Intensive Unit (RIU).

Patients and methods: A total of 39 PMV patients (13 in ICU and 26 in RIU) were included in the study. All patients were in stable condition, without need for sedation, with GCS > 10. All patients were tracheostomised under mechanical ventilation support at least during the night. A full PSG was performed in all patients during night sleep under PS ventilation.

Results: Sleep efficiency was higher in ICU (82.7±18.3%, RIU 68.4±21.8%, p=0.02) with longer sleep time (SPT ICU 448±62 min. RIU 346±56 min, p<0.001). Duration of stage N2 was 61.4±20.6% in ICU and 48.8±20.5% in RIU, with longer stage N3 in RIU (10.7±15.6%, ICU 5.7±12.6%), but these differences were not statistically significant. Yet, REM sleep duration was longer in RIU (10.3±6.8, ICU 3.7±4.9, p=0.01). Despite pressure support ventilation during night sleep, some breathing abnormalities appeared in RIU patients, with hypoxemia especially during REM (94.4±3.2%, ICU 98.3±6.0%, and apneas or hypopneas (AHI 3.34±11.6h).

Conclusions: Sleep quality was impaired in PMV patients during hospitalisation either in ICU or in RIU, but sleep structure approach normal architecture in RIU. REM sleep breathing abnormalities in RIU patients may require further clinical evaluation in terms of the efficacy of mechanical ventilation mode.

P5013
Swallowing disorders and speech rehabilitation in tracheostomized difficult-to-wean patients
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Background: Swallowing disorders often complicate long-term management of tracheostomised difficult-to-wean patients (DWPs) and may represent a common drawback to the removal of the cannula.

Aims: To evaluate the prevalence of swallowing disorders among DWPs and the restoration of proper swallowing after a weaning and pulmonary rehabilitation program including speech rehabilitation (SR).

Methods: 157 tracheostomised DWPs (83 males, age 69.9±12.5y), consecutively admitted, underwent dysphagia assessment including objective assessment, methylene blue test, and eventually fibroschopy swallowing evaluation.

Results: 74 patients (42 males, age: 70.4±12.5y), were evaluated at risk of aspiration, and underwent SR program. 25 patients, affected by severe ALS, and 15 affected by neurological disorders determining very severe cognitive impairment (GCS<9) were not included in the SR program. 57 (77.0%) out of 74 treated patients recovered swallowing function and were allowed to feed orally; 8 (10.8%) semiliquid, 17 (23.0%) semisolid, 14 (18.9%) homogeneous; 18 (24.3%) solid. In 10 patients compensatory postures were adopted. 13 patients were treated with pancutanous gastrostomy, 4 were discharged with nasogastric feeding tube. 30 patients (40.5%) underwent to tracheostomy decannulation. Length of stay was greater for dysphagic patients (21.7±12.7 vs 33.5±14.4, p<0.001).

Conclusions: Swallowing disorders showed high prevalence among DWPs and are related to an higher length of stay in hospital. Further research are needed in order to determine the burden of swallowing disorders in DWPs and evaluate the effectiveness of their treatment.

P5014
Review of decannulation experience and duration of tracheostomy within the Newcastle upon Tyne Hospitals NHS Foundation Trust
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Background: Tracheostomy is increasingly used to manage airway difficulties in paediatric respiratory management. It is important that parents are informed of the likely duration of tracheostomy in different conditions and the prognosis for decannulation.

Aims: The aim of this project was to review the experience of paediatric tracheostomy decannulation in the Newcastle upon Tyne Hospital NHS Foundation Trust (NUTH) Trust over the last 6 years.

Methods: This retrospective review looked at all decannulation episodes in children within the NUTH Trust from January 2005 to December 2010. The notes of the patients identified were reviewed to collect data.

Results: 56 patient episodes were identified, of those, 48 patients were included. The median duration of tracheostomy was 14 months and the median age at decannulation was 26 months. The indications for tracheostomy were: subglottic stenosis (31%), airway malacia (21%), airway mass (13%), airway obstruction (10%) and other (25%). The median duration for these indications were 35, 17.5, 8, 12 and 11.5 months respectively. 81.25% (39) of planned decannulations were successful. Surprisingly 61.54% (24) of successful decannulations had trachy-cutaneous fistulas requiring surgical closure. It appeared that fistulas were associated with patients who were of a younger age at tracheostomy (4.5 vs. 8 months) or who had a longer duration of tracheostomy (20 vs. 12 months).

Conclusions: This review has highlighted likely duration of tracheostomy for the common conditions and prognosis for decannulation. It has also revealed a surprisingly high rate of trachy-cutaneous fistula.

P5015
Prognostic factors for long-term survival in ICU tracheostomized patients
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Introduction: Few recent studies have evaluated the long-term prognosis of ICU patients who are tracheostomized for their underlying lung disease.

Patients and methods: We conducted a retrospective study from 1997 to 2010 in 82 patients who were tracheostomized during their stay in a medical intensive care unit (ICU). The main objective was the evaluation of long-term survival

Results: Among the 82 patients, 40 (48.8%) have a chronic respiratory failure (16 obstructive, 9 mixed and 15 restrictive with 11 neuromuscular disease). Fifty-nine patients (72%) died (50% before hospital discharge. The median survival time is 188 days. In multivariate analysis using the Cox model, three prognostic factors have been highlighted: 1) the presence of a neurological disease was significantly associated with a better prognosis (OR 0.48 [0.26-0.9], p = 0.022), 2) an age above 65 years (OR = 2.2 [1.17-4.16], p = 0.015) and 3) a Charlson score greater than 2 (OR = 2.05 [1.09-3.86] p = 0.026) were significantly associated with a poor prognosis. GOLD stage IV COPD was not associated with a poor prognosis (OR = 1.93 [0.98-3.81], p = 0.058). Bleeding or respiratory complications were found respectively in 16 (20%) and 7 (9%) patients. Among patients discharged from the hospital, the weaning of mechanical ventilation was obtained in 19 of 46 cases (41.3%).

Conclusion: We found two pejorative prognostic factors (age > 65 years and a Charlson score > 2) and one protective factor (presence of a neurological disease) significantly related to the long-term survival in ICU tracheostomized patients.

P5016
WITHDRAWN

917s
Assessment of rapid shallow breathing index as a predictor for weaning in respiratory care unit

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Introduction: Weaning is gradual removal of mechanical ventilator support. Different predictors are used for weaning initiation. This study is designed to investigate the rapid shallow breathing index (RBSI) as a predictor for successful weaning.

Materials and methods: We did this cross-sectional study on 70 patients who had mechanical ventilation for more than 48 hours in respiratory care unit (RCU) in Tehran Labbafi Nejad hospital. We measured RBSI, and then evaluate the value of RBSI for successful extubation.

Results: 63 (90%) Patients had RBSI ≤ 105 (Breath/min/L), among them 49 (77%) patients had successful weaning and did not need re-intubation but the rest had unsuccessful weaning (P=0.001). Weaning index mean for patients with successful extubation was 66±57.2 and for patients with unsuccessful extubation was 76.9±28.1. We could not find a significant difference between means (P=0.433).

Conclusion: Our findings exhibited that RBSI has high sensitivity with low specificity. RBSI ≤ 80 is more reliable than RBSI ≤ 105 as a predictor for weaning.
OPYS1

Immunomodulatory function of chemerin and its receptor ChemR23 in the physiopathology of viral pneumonia and acute lung injury

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Background: The role of chemerin (ChemR23) in the modulation of innate and adaptive immune responses is not fully understood. This receptor has been shown to stimulate pro-inflammatory responses in macrophages and dendritic cells, which could be important in viral infections.

Methods: We investigated the role of ChemR23 in the modulation of the immune response to respiratory virus infection in mice. We used wild-type (WT) and ChemR23−/− mice infected with either respiratory syncytial virus (RSV) or influenza A virus (IAV). The immune response was analyzed by measuring cytokine levels, leukocyte infiltration, and pathological changes.

Results: In WT mice infected with RSV, ChemR23−/− mice had reduced leukocyte infiltration and decreased cytokine production compared to WT mice. In contrast, in IAV-infected mice, ChemR23−/− mice had increased leukocyte infiltration and cytokine production. Overall, our data suggest that ChemR23 plays a role in modulating the immune response to respiratory virus infection, with different effects depending on the virus and the stage of infection.

Conclusion: Our findings highlight the importance of ChemR23 in the modulation of the immune response to respiratory virus infection and suggest potential therapeutic targets for the treatment of viral pneumonia and acute lung injury.

OPYS2

Role of Th9 cells in allergic airway inflammation induced by house dust mite

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Interleukin (IL)-9-secreting Th9 cells play a key role in the modulation of allergic responses. However, the specific function of Th9 cells in allergic airway inflammation is not fully understood. In this study, we investigated the role of Th9 cells in the allergic response to house dust mite (HDM) exposure.

Methods: We used BALB/c mice sensitized and challenged with HDM to induce allergic airway inflammation. Th9 cell numbers and function were measured in vivo and in vitro, and the role of Th9 cells in regulating allergic airway inflammation was assessed by adoptive transfer experiments.

Results: Th9 cells were increased in the bronchoalveolar lavage fluid (BALF) of HDM-challenged mice, and adoptive transfer of Th9 cells to naive mice induced allergic airway inflammation. Th9 cells were shown to produce IL-9, which is essential for the development of Th2 responses.

Conclusion: Our findings suggest that Th9 cells play a critical role in the development of allergic airway inflammation induced by HDM exposure. Understanding the specific function of Th9 cells in allergic airway inflammation could provide new targets for the treatment of allergic diseases.

OPYS3

Thymic stromal lymphopoietin is a central regulator of anti-viral CD8+ T cell response

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Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine that is primarily produced by epithelial cells at mucosal surfaces. It has been widely studied in Th2-driven inflammatory disorders such as atopic dermatitis and asthma. Although both viral nucleic acid analogues and pro-inflammatory cytokines associated with active viral infections are potent stimulators of TSLP expression in vitro, its role in antiviral immunity is unknown. To elucidate the role of TSLP in viral infections, we investigated the immune response against influenza A in mice deficient in TSLPR. We found that TSLPR-deficient mice exhibited impaired clearance of the virus at late time points post infection, indicative of a defect in the adaptive immune response. Although priming in the lymph node was unaffected, the virus-specific CD8+ T cell response in the lung was compromised in the absence of TSLPR. This defect was characterized by the reduced frequency of virus-specific CD8 T cells as well as reduced effector functions such as granzyme B expression and interferon γ production. Using mixed bone marrow chimeras and adoptive transfer studies, our data suggest that TSLP affects influenza-specific responses by modulating the function of recruited inflammatory dendritic cells (DCs). Pulmonary DCs isolated from infected lungs of TSLPR deficient mice were defective in inducing proliferation of antigen-specific naive T cells in vitro. Furthermore, in the absence of TSLPR the production and trans-presentation of IL-15 by CD11b+ inflammatory DC was impaired. We propose that TSLP regulates activation of antigen specific cytotoxic T cells at the site of infection by modulation of DC function and suggest a crucial link between TSLP and IL-15 production during infection.

OPYS4

Regulation of allergic airway disease by IL-4/IL-13 activated macrophages and dendritic cells

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While IL-4Rα and its ligands IL-4 and IL-13 play an important role in mouse models of allergic airway disease, the effects of IL-4 and IL-13 signaling through specific cell types are unclear. The generation of mice with cell specific impairments of IL-4Rα on macrophages/neutrophils (Ly5+IL-4Rα+/-) and dendritic cells/macrophages (CD11c+IL-4Rα+/-) has enabled us to investigate the effect of IL-4/IL-13 signaling on macrophage and dendritic cell function in allergic airway disease.

IL-4Rαlox/−, IL-4RαCre+IL-4Rαlox/−, and Ly5+IL-4Rαlox/− mice were sensitized and challenged with ovalbumin. OVA-challenged IL-4Rαlox/− mice had increased airway resistance and elastance, lung inflammation, and mucus hypersecretion compared to PBS controls. In IL-4Rαcre+ mice, airway resistance and elastance, mucus hypersecretion, Th2 responses and eosinophil infiltration was decreased. However, in both Ly5+IL-4Rαlox/− mice and CD11c+IL-4Rαlox/− mice, airway resistance and elastance were slightly increased. This indicates that IL-4/IL-13 activated macrophages may play a role in downregulating allergic airway disease. Furthermore, lung CD4+ T cells from CD11c+IL-4Rαlox/− mice but not Ly5+IL-4Rαlox/− mice had significantly increased production of the Th2 effector cytokines IL-13 and IL-5 as well as significantly increased lung eosinophils and neutrophils, suggesting an additional role for IL-4/IL-13 activated dendritic cells in downregulating Th2 responses and granulocyte infiltration into the lungs. In summary, we find a role for IL-4/IL-13 signaling through both macrophages and dendritic cells in regulating allergic airway disease in mice.

OPYS5

The influence of glucocorticoids on transcription factor balance in asthma patients

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Background: Transcription factors are important in T-cell subset differentiation as well as clonal expansion and determine the polarization process towards different T cell phenotypes. Glucocorticoids are important for asthma treatment, potentially by modulating T cell differentiation. We hypothesize that the transcription factor balance could be of predictive value in the treatment of asthma. Our study aimed to profile T-cell transcription factors after 8 week GC-treatment of steroid naïve
asthmatic patients and to test the steroid sensitivity of Th2 versus Th1 and Treg transcription factors (TF) after a treatment period, which is known to control Th2-cell activity and improve clinical symptoms.

Methods: Human CD4+ T-cells isolated from steroid naive atopic asthmatic individuals and decreased significantly following GC treatment. In vitro analysis revealed that Gfi-1 is abundantly expressed in Th2-polarizing conditions in asthma and displays dose-dependent sensitivity to GCs. The current study shows for the first time that Gfi-1 is involved in allergic asthma and may represent a biomarker for assessing Th2-dependent disease and GC-responsiveness.

OP1 Neutrophils augment LPS-mediated pro-inflammatory signaling in human lung epithelial cells

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The role of polymorphonuclear neutrophils in pulmonary host defense is well recognized. The influence of a pre-existing neutrophilic inflammation on airway epithelial response towards pro-inflammatory triggers, however, is still poorly understood. Therefore, aim of this study is to investigate the effect of neutrophil-induced LPS on pre-existing pro-inflammatory signaling in lung epithelial cells. Human bronchial epithelial cells (BEAS-2B) were incubated with human peripheral blood neutrophils or bone-marrow derived neutrophils from C57Bl/6J wildtype or NADPH-oxidase deficient (p47<sup>−/−</sup>/murine). Upon LPS stimulation, IL-8 production and reactive oxygen species (ROS) generation were measured. Additionally, activation of extracellular regulated kinases (ERK)1/2 and nuclear factor (NF)-κB signaling pathways was analyzed.

Our studies show that neutrophils synergistically increases LPS-induced IL-8 and ROS production by BEAS-2B cells without inducing cytoxicity. The observed IL-8 response to endotoxin increases in proportion to time, LPS-concentration and the number of neutrophils present. Moreover, this synergistic IL-8 production correlated with the chemotactic properties of the co-incubations and significantly depended on a functional neutrophilic NADPH oxidase. The presence of neutrophils also augments LPS-induced phosphorylation of ERK1/2 and IκBα as well as NF-κB RelA DNA binding activity in BEAS-2B.

Our results indicate that the pro-inflammatory effects of LPS towards lung epithelial cells are amplified during a pre-existing neutrophilic inflammation. These findings support the concept that patients suffering from pulmonary neutrophilic inflammation are more susceptible towards pro-inflammatory triggers.

OP2 Angiostatin inhibits neutrophil migration and activation

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Angiostatin inhibits neutrophil migration and activation

Additionally, activation of extracellular regulated kinases (ERK)1/2 and nuclear factor (NF)κB signaling pathways was analyzed.

Background: A novel immunomodulatory phenotype has recently been identified in human neutrophils that is characterized by diminished chemotaxis in response to fMLP and LPS. ANG also inhibited the signal for phosphorylated p38 MAPK in phagocytosing neutrophils.

Results: ANG inhibited neutrophil rolling flux (<i>p</i>&lt;0.05) in capillary vessels in TNFα-treated cremaster muscles. We conclude that ANG is a novel inhibitor of neutrophil migration and activation. (Funding NSERC Discovery Grant)

OP3 Production of alpha-1 antitrypsin (AAT) by pro- and anti-inflammatory macrophages and dendritic cells

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Acute exacerbations (AE) in COPD have been frequently associated with respiratory infections. However, a causal relationship is debatable as bacteria can also be found in stable patients. To explain this discrepancy, differences in bacterial strain virulence have been suggested. To test this, we examined the virulence of different <i>Haemophilus</i> strains, isolated from COPD patients, either in a stable phase or during an AE.

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OP6
Endogenous transforming growth factor beta (TGF-β) influences rhinovirus (RV) replication in primary bronchial epithelial cells (PBECs) by suppressing the innate immune response
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RV infection is a major cause of asthma exacerbation in children and adults. PBECs from asthmatics have a deficient IFN response against RV infection, the molecular mechanism of which is unknown. TGF-β is an anti-inflammatory cytokine which is highly expressed in asthmatic tissue and augments RV replication in bronchial fibroblasts by decreasing the innate immune response (Thomas BJ 2009)

Objective: To determine whether the presence of endogenous TGF-β in cultured PBECs from asthmatic patients augments RV replication.

Method: We measured endogenous TGF-β levels in serum-free media from normal and asthmatic PBECs. PBECs from both groups were pretreated with 10 ng/ml neutralizing anti-TGF-β antibodies and infected with RV1B for 24 or 48 hrs. We measured virus titres by TCID50/ml and levels of IFN-β, IP-10 and RANTES protein by ELISA. SOCS-1 and SOCS-3 mRNA levels were quantified by RT-qPCR.

Results: Endogenous TGF-β was higher in asthmatic PBECs than in normal PBECs. Inhibition with a specific antibody to TGF-β in a greater decrease in RV replication in asthmatic PBECs than in normal PBECs. This was accompanied by increased IFN-β protein relative to virus particles. IFN-β and IFN-λ protein levels were upregulated when asthmatic PBECs were treated with anti-TGF-β and polyIC. The antibody significantly decreased SOCS-1 and SOCS-3, which control IFN responsiveness. It had no significant effect on RV-induced IP-10 and RANTES protein production.

Conclusions: Our results suggest that high levels of TGF-β in asthmatics may contribute to a deficient innate immune response to RV infection by decreasing IFN production.

PP101
Critical role of IL-25 in initiation of airway remodeling during a house dust mite driven model of disease
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Airway epithelial cells are key contributors to the innate immune system and intimately involved in allergen recognition and in modulating allergic immune responses. IL-25 is secreted by airway epithelium and is implicated in the regulation of asthma. Using an adenoviral vector to overexpress the TGF-β and activin signalling molecule Smad2 in the airway epithelium enhances airway remodelling and AHR in mice exposed to the environmental allergen house dust mite (HDM). We thus determined whether a neutralising antibody to IL-25 could influence disease pathology induced by HDM following this perturbation of the pulmonary epithelium. AHR was significantly reduced in both the AdSmad2 and AdC (empty vector) mice exposed to HDM. Similarly, peribronchial collagen deposition in HDM treated mice was also reduced (p=0.05). CCL20, a sentinel chemokine that alerts and recruits innate and adaptive immune cells to the lung, was also reduced to baseline values in mice treated with anti-IL-25 even in mice overexpressing epithelial Smad2. Pulmonary levels of the ‘alarmin’ IL-33, known to be important for innate-type mucosal immunity in the lungs and TSLP were also completely abrogated. Elevation in the prototypical Th2 cytokines IL-4, -5 & -13 was reduced following exposure to HDM (p<0.05), however they were still significantly elevated compared to controls. Thus, blocking IL-25 prevented the increase in innate epithelial derived cytokines and reduced the severity of AHR in response to HDM in both control mice and those with an altered, ‘pro airway remodelling’ epithelial phenotype. Understanding allergic innate immunity could potentially lead to new therapeutic targets for the treatment of asthma.

PP102
GOB4/AGR2 deficiency protects against allergic airway disease
Charlene DeClercq1, Lawrence Mason 1, Nancy Stedman 1, Edward Lavallie2
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Introduction: GoBlet cell gene 4 (GOB4), a.k.a. anterior gradient homolog 2 (AGR2), is a protein disulfide isomerase restrictedly expressed by goblet cells of the airways and the lung.

Objectives: Because GOB4 expression is essential for mucus production in the gut, we hypothesized that it also modulates aspects of allergic airway disease (AAD), including mucus secretion.

Methods: First we focused on a classic model of ovalbumin (OVA)-induced AAD.

In a second set of studies, mice were exposed intranasally (IN) to recombinant murine (rMII-13), which induces a 10-fold increase in GOB4 mRNA expression in the lung. Bronchoalveolar (BAL) lavage and tissue samples were collected 24h and 48h post-rMII-13 or OVA challenge, respectively.

Results: In mice sensitized and challenged with OVA, BAL cellularity was significantly reduced in GOB4 deficient mice compared to wild-type (WT) controls (p=0.009). This was mainly due to lower numbers of eosinophils (p=0.0012) and lymphocytes (p=0.0017). Incidence and severity of intrabronchial mucus accumulation were also lower in tissues from GOB4 deficient mice. In the second protocol, WT mice exposed to rMII-13 developed airway neutrophilia, histiocytic and lymphocytic inflammation, goblet cell metaplasia with intracellular mucus plugs, and vascular mural hypertrophy. In contrast, GOB4 deficient mice exposed to rMII-13 developed neither the airway inflammation nor the morphological changes observed in their WT counterparts.

Conclusion: Our data indicate that, in AAD conditions, GOB4 deficiency protects not only against mucus-driven aspects of the disease but also largely from allergic airway inflammation, making GOB4 an attractive target for the treatment of asthma.

PP103
Steroid-insensitive expression of CCL17 from asthmatic lung macrophages: a driver of severe disease?
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2. Southampton Respiratory NIHR Biomedical Research Unit, Southampton, Hampshire, GB

Asthma is a complex inflammatory disease of the airways characterised by an increase in the number of CD4+ helper T cells within the lung. The Th2 cytokine IL-4, can also change the phenotype of macrophages. These M2 macrophages are characterised by increased expression of the cell surface marker CD206, as well as being sources of the Th2 cell chemokine CCL17. We hypothesised that it is the macrophage that is the main source of CCL17 in the asthmatic airway.

Using sputum macrophages purified by flow cytometry from the airways of 11 healthy controls and 11 asthmatics, we observed increased expression of CCL17 mRNA (p=0.0311). In contrast, there was no difference in CCL17 expression as assessed by flow cytometry. Furthermore, upon culture bronchoalveolar lavage (BAL) cells from asthmatics released more CCL17 than healthy control cells. Interestingly, this higher expression of CCL17 is also observed in samples derived from moderate asthmatics who were treated with inhaled steroids.

We tested the efficacy of the steroid fluticasone propionate on inhibiting CCL17 release from monocyte-derived macrophages treated with IL-4. We observed that the steroid had no effect on CCL17 release even at high concentrations (10 μM).

In contrast, release of CCL17 was inhibited when the cells were exposed to the PI3-Kinase inhibitor, LY294002 (10 μM).

Taken together, these data indicate that expression of CCL17 in lung macrophages from asthmatics is steroid insensitive and that lung macrophages may be partially responsible for driving the disease. In addition, therapeutics targeting the PI3-Kinase signalling pathway may improve control of the disease in severe steroid-insensitive forms of asthma.

PP104
Short-chain fatty acids are potent modulators of allergic airway inflammation
Aurélien Trompette1,2, Anke Sichelstiel 1,2, Koshika Yadava 1,2
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Introduction: Over the past few decades, there has been a dramatic increase in the prevalence of asthma in westernized countries. Both experimental and epidemiological data indicate that environmental factors, such as an individual’s diet and communal flora can have profound effects upon the susceptibility and progression of inflammatory diseases.

Rationale: There is a growing body of evidence showing that the gut microbiota can influence immune responses. Short-chain fatty acids (SCFAs), end-products of the colonic fermentation of dietary fibers by bacteria, have been shown to exert protective effects upon cardiovascular and intestinal inflammation; however, their impact upon lung inflammation remains to be determined.

Methods: C57Bl/6 mice were given individual SCFAs in drinking water or intraperitoneally 2 weeks prior to and throughout the induction of aFel d1-induced acute model of allergic asthma. As an alternative method, mice were fed a low-fiber diet from birth to reduce circulating levels of endogenous SCFAs.

Results: Mice exposed to SCFAs exhibited reduced airway inflammation, characterized by a significant reduction of infiltrating eosinophils (39.8±6.9% vs. 4.2±5.3%; p<0.01) in the bronchoalveolar lavage, in addition to significantly less systemic Fel d 1-specific IgE and IgG1 antibodies (1.41±0.2 vs. 0.37±0.02 and 1.36±0.1 vs. 0.52±0.2, respectively). Interestingly, mice that were fed a low-fiber diet exhibited an exacerbated airway inflammation when exposed to the Fel d 1 allergen.

Conclusions: Our results show that SCFAs have intrinsic immunomodulatory functions with the ability to dampen lung inflammation in a mouse model of acute allergic asthma.
PP105  
Changes in the proteome upon dermal sensitization in a mouse model of chemical-induced asthma  

Steven Haenen1, Elke Clynen2, Vanessa De Vooget1, Peter Hoet3, Ben Nemery1,  
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In follow-up of our studies on proteomic changes in a validated mouse model of immunologically mediated chemical-induced asthma, using tritiated thymidine (TDR) as a sensitizer [1], we evaluated the temporal changes at early time points following dermal sensitization. The identification of biomarkers of sensitization could help to move diagnosis to an earlier (pre-clinical) stage. We explored the proteome of the auricular lymph nodes and serum of mice dermally sensitized to TDI.  

Mice were treated once (day 1) or twice (day 1 and 8) with TDI or with the vehicle (acetone-olive oil, 2:3, control) on both ears. Auricular lymph nodes and serum were collected three days later. Two-dimensional difference gel electrophoresis was used to analyze the differential proteins (p<0.01) of TDI-sensitized mice vs. control mice (p<0.12). Proteome analyses of the auricular lymph nodes resulted in 39 and 86 differential proteins and of serum in 7 and 16 differential proteins, after 1 and 2 sensitizations, respectively. Identification (MALDI-TOF MS) of these proteins mainly showed structural (e.g. vimentin), immune related (e.g. lymphocyte specific protein-1) and oxidative stress related proteins (e.g. peroxiredoxin 6) in both the lymph nodes and the serum.  

Now, a software based pathway analysis of the differentially expressed proteins is performed (Anadate Genomics). This will give more insight in the cellular and molecular events involved in early sensitization, leading to chemical-induced asthma. Possible biomarkers among the differential proteins will be validated.  

References:  

PP106  
P2Y2 receptor regulates VCAM-1 membrane and soluble forms and eosinophil accumulation during lung inflammation  

Gilles Vanderstocken1, Benjamin Bondue1, Michael Horckmans1, Larissa De Pooter2, Jean-Marc Roys3, Jean-Marc Roys2, Jean-Marc Roys3, Didier Communs1,  
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ATP has been defined as a key mediator of asthma. In this study, we evaluated lung inflammation in mice deficient for the P2Y2 purinergic receptor. We observed that eosinophil accumulation, a distinctive feature of lung allergic inflammation, was defective in OVA-treated P2Y2-deficient mice compared with OVA-treated wild type animals. Interestingly, the upregulation of VCAM-1 was lower on lung endothelial cells of OVA-treated P2Y2−/− mice compared with OVA-treated wild type animals. Adhesion assays demonstrated that the action of UTP on leukocyte adhesion through the regulation of endothelial VCAM-1 was abolished in P2Y2−/− lung endothelial cells. Additionally, the level of soluble VCAM-1 reported as an inducer of eosinophil chemotaxis, was strongly reduced in the anti-GR1 antibody (aGR1) or HBSS on day13. On day 15, they received an oropharyngeal cyclophosphamide (CP) or saline on days 11 and 13, or 1 intravenous injection of cyclophosphamide (CP) and aGR1 induced a full neutrophil and eosinophil depletion in both BAL and blood. CP led to a complete disappearance of the TDI-induced AHR, while aGR1 caused only a partial decrease in AHR. CP-injected mice showed an almost full depletion of the auricular lymphocytes, while this was only slightly decreased in the aGR1-injected TDI-mice, mainly caused by depletion of T-lymocytes (CD3+). A decrease of the concentration of IL-3 was detected in the aGR1-injected TDI-mice compared to the HBSS-injected TDI-mice. A decreased total serum IgE was observed only in CP-injected TDI-mice.  

In conclusion, CP and aGR1 are potent neutrophil depletion agents, which clearly influence AHR in our mouse model of chemical-induced asthma. However, because these agents also impact other cells the specific role of neutrophils could not be clarified.  

PP108  
Resolution of house dust mite (HDM) induced allergic airways disease  

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The debilitating symptoms of impaired lung function and mucous secretion experience by asthma patients can persist for several days following allergen exacerbation. This persistence may occur due to deficiencies in specific pro-resolving mediators thereby contributing to the propagation of chronic inflammation. The purpose of this study was to characterise the resolution of allergic pulmonary inflammation in mice following 3 weeks of intranasal challenge using HDM. Disease parameters were measured at 4 hours, 7 days and 13 days following cessation of allergen exposure. Airway hyperreactivity (AHR) was sustained at 7 days post challenge compared to PBS treated controls, returning to baseline by 13 days (Resistance at 100μmH<sub>2</sub>O was 5.73 ± 0.41 vs. 3.20 ± 0.19, P<0.05). This was accompanied by persistent levels of Th2 lymphocytes (2.63 ± 10<sup>5</sup> cells/ml and 1.32 ± 10<sup>5</sup> cells/ml vs. 0.79 ± 10<sup>5</sup> cells/ml, P<0.05) and eosinophils (18.9 ± 10<sup>5</sup> cells/ml and 7.16 ± 10<sup>5</sup> cells/ml, vs. 1.8 ± 10<sup>5</sup> cells/ml, P<0.001), returning towards baseline by 13 days. The Th2 lymphocyte numbers did not correlate with the epithelial derived cytokine, IL-33, which returned to baseline by 7 days. Histological analysis of lung sections stained with Periodic-acid Schiff show that mucus persists up to 13 days. The pro-resolving lipid, Lipoxin A4 is expressed in the lung at 4 hours and remained detectable up to 13 days. CD200R is expressed on myeloid cells and has been implicated in the maintence of pulmonary immune homeostasis. Following HDM exposure, expression of CD200R on alveolar macrophages peaked at 7 days and remained elevated at 13 days. These data indicate that distinct molecular pathways may be responsible for induction and maintenance of allergic inflammation and AHR.  

PP109  
Different biochemical properties of house dust mite induce divergent epithelial and inflammatory responses  

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Introduction: Allergic asthma is mainly caused by exposure to aeroallergens like house dust mite (HDM), when transepithelial delivery is facilitated by disruption of the epithelial barrier.  

Objective: We aimed to gain more insight in which biochemical property of HDM is critical for the disruption of barrier function and initiates an inflammatory response.  

Methods: HDM extracts with different biochemical properties were analyzed for their effects on airway/bronchial epithelial barrier function by measuring changes in transepithelial resistance and immunostaining of the functional proteinsZO-1, occludin and E-cadherin. Furthermore, we examined the induction of a pro-inflammatory phenotype of human bronchial epithelium by these HDM extracts, as well as the epithelial remodeling and airway inflammation in vivo in a mouse model.  

Results: We found that the different HDM extracts induced divergent responses. Importantly, the extract with lowest serine protease activity induced the most pronounced effects on barrier function in vitro, and induced an increased production of the pro-inflammatory chemokine CCL20. Remarkably, the same HDM extract induced HDM-specific IgE, a profound epithelial E-cadherin delocalization, goblet cell hyperplasia, cellular inflammation and increased levels of CCL17 and IL-5 in vivo.  

Conclusion: Together, these results indicate that the disruption in epithelial barrier function is independent of serine protease activity, and is essential for allergic sensitization and airway remodeling in vivo.  

PP110  
The role of IL-25 in rhinovirus-induced asthma exacerbations  

Janine Beale, Nathan Bartlett, Sebastian L. Johnson. Imperial College London, Respiratory Medicine, National Heart and Lung Institute, UK  

Rhinoviruses (RV) are the major causative factor of asthma exacerbations (AE). While Th2-mediated inflammation is implicated in asthma, it is unknown how the
immune response to RV infection interacts with Th2 immunity causing an AE. Mast cell-deficient IL-25 is an important regulator of Th2 immunity and plays a role in asthma pathogenesis. We hypothesized that RV infection of the epithelium induces IL-25 production facilitating immunopathogenesis of AE. We measured IL-25 mRNA in mouse models of RV infection and RV-induced exacerbation of allergic airway inflammation [1]. In vitro IL-25 gene induction was also assessed in allergic asthma tissue-incepted mast cells (BEC) infected with RV and stimulated with IL-4 in vivo and in vitro results demonstrated that RV induced IL-25 mRNA as measured by qPCR. Airway challenge with ovalbumin (OVA) followed by RV infection in sensitized mice exacerbated allergic airway inflammation and coincided with enhanced IL-25 mRNA expression compared with allergen or infection alone. Similarly, RV and IL-4 treatment of BECs resulted in the highest levels of IL-25 mRNA. The novel finding that RV infection induces IL-25 represents a link between antiviral responses and Th2 inflammation identifying a role for IL-25 in RV-induced AE. Allergen/IL-4 treatment enhanced RV-dependent IL-25 expression thus a Th2 environment and virus may result in exacerbated Th2 inflammation mediated by IL-25.

Reference:

PP111
Mast cell distribution influences airway inflammation and hyperresponsiveness in a chronic model of asthma

Barbara Fuchs1,2, Lisa Sjöberg1,2, Christine Möller Westerberg2, Linda Swedin1, Sven-Erik Dahlén1, Mikhail Aurer1, Gunnar Nilsson2, Sven-Erik Dahlén1, Mikael Adner1, Gunnar Nilsson2.

In asthma pathogenesis, mast cells (MCs) may play a divergent role for allergic inflammation and airway hyperresponsiveness. Spatial location of MCs can contribute to symptom severity.

MC-deficient C57Bl/6 Kit-w/w-sh mice (ko), bone marrow-derived MCs reconstituted C57Bl/6 Kit-+/+ mice (bmmc-+/+) and wild-type controls (wt) were investigated in a 91-day ovalbumin model of chronic allergic airway inflammation.

Toluoline blue stained lung sections demonstrated a increased number of MCs in bmmc-+/+ mice compared to wt. Moreover, MC distribution differed between the study groups: in wt mice, MCs were located around central airways, while prominently found in the parenchyma and around smaller airways in bmmc-+/+ mice. These findings subsequently influenced important parameters: In BALF, total cell, eosinophil and neutrophil counts, were most pronounced in MC-deficient mice. Therefore, a protective role of MC in the manifestation of chronic inflammation is suggested.

Measurement of AHR using forced-oscillation technique revealed an increased hyperresponsiveness in the absence of MCs in the lung. In addition, the absence of MCs in the lung periphery exaggerates tissue reactivity, however, an increased number of bone-marrow derived MCs in the periphery even adds to the effect of MCs in the lung.

MCs can modulate processes leading to airway inflammation and airway hyperresponsiveness by their mere number, their tissue distribution, and possibly also their phenotype.

PP112
Stability of biomarkers in severe asthma – 1 year follow up study

Maciej Kupczyk1, Roelinde Middelveld1, Barbro Dahlén2, Sven-Erik Dahlén1.

In order to test the hypothesis of stability of phenotypes 93 patients with severe asthma (SA), 76 with mild-to-moderate asthma (MA) and 64 with COPD were screened and included in the BIOAIR study. The variable in clinical outcomes and biomarkers was followed for 1 year. Comparison of baseline vs 1 year revealed that there were no changes in QoL, FIV1/FVC and eNO in any of studied cohorts. There was a trend for decrease in FEV1 in % in MA and COPD patients but not in SA. The FEV1/FVC ratio decreased by 3% in SA (69.4±3 vs 66±1.2%, p=0.006, mean±SE). We found an increase in C-reactive protein in SA (3.6±6.1 vs 8.4±4.9 mg/ml, p=0.025), decrease in sputum eosinophils in MA (62.5±27.6 vs 49.9±21.9%, p=0.047) and increase in sputum eosinophils in COPD patients (0.8±1±1 vs 2.4±2.6%, p=0.01). There was no change in mean urinary LTE 4 concentration in EBC after 60 and 120 min after administration, comparing to placebo (5.34±3 μg/mmol (60 min), and 5.23±3 μg/mmol (120 min)) respectively. No influence of apocynin on safety parameters, and no adverse effects has been observed.

These data suggest that using apocynin might be a promising solution to alleviate inflammatory process, and probably, symptoms of inflammatory diseases.

PP114
Effect of inhaled apocynin on reactive oxygen species concentrations in exhaled breath condensate of asthmatics

Joanna Stefanska1, Agata Sarnicka2, Anna Wlodarczyk3, Milena Sokolowska1, Zbigniew Doniec4, Bartosz Nowak5, Rafał Pociejczak1.

In asthma pathogenesis, mast cells (MCs) may play a divergent role for allergic inflammation and airway hyperresponsiveness. Herenic, RV infection in sensitized mice exacerbated allergic airway inflammation and coincided with enhanced IL-25 mRNA expression compared with allergen or infection alone. Similarly, RV and IL-4 treatment of BECs resulted in the highest levels of IL-25 mRNA. The novel finding that RV infection induces IL-25 represents a link between antiviral responses and Th2 inflammation identifying a role for IL-25 in RV-induced AE. Allergen/IL-4 treatment enhanced RV-dependent IL-25 expression thus a Th2 environment and virus may result in exacerbated Th2 inflammation mediated by IL-25.

Background: Some epidemiologic studies have indicated that attendance to chlorinated swimming pools is associated with bronchial hyperreactivity, allergies and asthma.

Aim: To investigate the effects of NaClO, the main pool disinfectant, on allergic sensitization and airway responses in mice.

Methods: Male BALB/c mice received 1 to 7 nasal instillations of ovalbumin (OVA, 1%) on alternate days 10 min after instillation of NaClO (3 ppm active chlorine) or water. 48h after, 1, 3, 5 and 7 instillations, we measured airway reactivity to methacholine (Flexivent), cellular inflammation in broncho-alveolar lavage (BAL), lung cytokines, and serum OVA-specific IgE. Later, methacholine reactivity 48 h after a single combined NaClO-OVA exposure was assessed in mice pretreated with the neurokinin1 receptor antagonist RP67580, in knock-out mice deficient in the transient receptor potential (TRP) channel A1 (TRPA1−/−) or 1 (TRPV1−/−) and in mast cell deficient mice (Kit-w/w-Kit-w/−sh).

Results: Combined nasal NaClO-OVA exposure induced airway hyperreactivity (AHR) to methacholine in the absence of airway inflammation and OVA specific IgEs. AHR was already induced after a single combined exposure to NaClO-OVA and it was not observed after either OVA or NaClO alone. The AHR response was reduced after pretreatment with RP67580. NaClO-OVA induced AHR in TRPV1−/− mice, but not in TRPA1−/− mice.

Conclusion: Combined nasal NaClO-OVA exposure induces AHR in the absence of allergic inflammation. This effect appears to involve TRPA1, mast cells and release of substance P, suggesting a neuro-immune interaction.
families of receptors are one of the key components of the innate immune system. 

The function of these receptors has been linked with susceptibility towards the development of allergic diseases, including asthma, making the TLRs and NLRs good targets for novel effective therapies of allergic diseases. In this study the mRNA expression levels of different TLRs and NLRs in the lung tissue in mild and severe mouse models of allergic asthma were measured by q-PCR. In addition, broncho-alveolar lavage fluid (BALF) was collected and cell numbers counted. Increased in the mild and severe asthma models different TLR and NLR mRNA expression profiles are observed. In the severe asthma model, a higher cell influx in BALF is seen. Moreover, a significant correlation is found between the mRNA expression of TLR3, TLR6 and TLR9 and the total cell number in the BALF.

PP116 Association of IL-9 and IL-4R genes and their Phenotypes among Sudanese with Asthma

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Background: Asthma is a complex heritable disorder, candidate genes that may be involved in the pathogenesis of asthma including interleukin 4 (IL-4), IL-5, IL-9, and IL-13 (Postma et al. 1995). Asthma prevalence in Sudan was found to be 12.5% in children aged 13-14 year in the Capital Khartoum (Mohamed et al. 1999).

Objectives: To detect polymorphisms of IL-9 in chromosome 5 and IL-4R in chromosome16 contributing to asthma and to estimate the environmental components. Total immunoglobulin E levels, skin prick test, and eosinophil count in Sudanese population.

Methods: Seventy, nuclear and extended families were sampled in the initial phase of the study. Ventilatory function, skin, prick test blood sample for DNA analysis, immunoglobulin E, eosinophil count were carried out in the whole sample. Genotyping for IL-9 and IL-4R polymorphisms using PCR were also carried out for a subset of the sample.

Results: Phenotypic analyses of the pedigrees suggest a likely genetic cause for a subset of the sample.

Conclusions: Asthma runs in families showing strong linkage to genes. There seems to be sufficient phenotypic and genotypic indicators to suggest a genetic predisposition component to asthma among Sudanese, and warrant some further investigations.

PP117 Behavioural and structural differences in migrating peripheral neutrophils from patients with COPD

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COPD neutrophils may behave differently than controls when migrating. This is important, as altered migration could drive pathological accumulation and lung damage.

Methods: We assessed neutrophil migration in 20 COPD patients, 20 healthy subjects (10 healthy smokers, 10 healthy never-smokers) and 20 patients with Alpha 1-Antitrypsin Deficiency (AATD).

Results: There were no differences in migration, structure or receptor expression in healthy smokers and non-smoking controls. COPD neutrophils moved with greater speed but reduced accuracy to all stimuli. E.g. fMLP: Speed, COPD μm/s (14.7±2.2) vs. healthy μm/s (10.5±0.8), P<0.001. There were no differences in receptor expression. E.g. α1-MLP: COPD 17.2 MFI (16-18 IQR), AATD 14.5 MFI (13-15), Healthy control, 16.2 MFI (10-30). Pseudopod formation and surface expression of mediator receptors were assessed. Neutrophils were incubated with their own, healthy control and COPD plasma, to determine if aberrant migration was inducible (with COPD plasma) or irreversible (with control plasma).

Conclusions: There were no differences in migration, structure or receptor expression in healthy smokers and non-smoking controls. COPD neutrophils moved with greater speed but reduced accuracy to all stimuli. COPD neutrophils moved with greater speed but reduced accuracy to all stimuli. AATD migrated more slowly than healthy controls, as indicated by a lower MFI for fMLP (17.2 vs. 14.5 MFI). Healthy neutrophils migrated with greater speed and accuracy than COPD neutrophils, as indicated by a higher MFI for fMLP (16.2 vs. 14.5 MFI). The results of this study suggest that COPD neutrophils may have altered migration that could contribute to the pathogenesis of COPD.

PP118 Inflammation and COPD: Protective effect of the recombinant anti-protease trappin-2 A26L, on lung epithelium

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Introduction: Inflammation in chronic obstructive pulmonary diseases (COPD) results in a protease-anti-protease imbalance that leads to a massive release of neutrophil serine proteases (cathepsin 3 and cathepsin G). These proteases stimulate secretion of mucus and pro-inflammatory cytokines. In order to target serine proteases, we designed a recombinant inhibitor derived from trappin-2 which is able to inhibit all three proteases at the same time. The aim of the study was to evaluate the inhibitory, anti-inflammatory and anti-secretory effects of trappin-2 A26L on lung epithelium exposed to neutrophil serine proteases.

Methods: A549 cells were exposed to proteases for 24h with or without addition of T2A6L. Protective effect of T2A6L towards the degradation of cell junctions by proteases was analyzed by immunofluorescence. Levels of mucus secretion were determined by measuring the rate of expression of mucus genes and the anti-inflammatory activity of T2A6L was investigated by measuring the rate of pro-inflammatory mediators release after LPS stimulation.

Results: Neutrophil serine proteases proteolytically degrade cellular junctions and increase mucin gene expression. T2A6L added to the culture medium inhibits the degradation of cell junctions proteins (E-cadherin, ZO-1), decreases MUC5AC and MUC1B mRNA expression induced by elastase and IL-6 and IL-8 productions.

Conclusion: Our results demonstrate that T2A6L exhibits anti-protectolytic, anti-inflammatory and anti-secretory effects. This new, anti-protease may therefore be of therapeutic value in treating inflammatory lung diseases.

PP119 Lymphangiogenesis in chronic obstructive pulmonary disease (COPD)

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Introduction: Lymphangiogenesis has been reported to be driven by mediators (e.g. hyaluronic acid) and inflammatory cells (e.g. activated CD11b+ macrophages), both commonly met in COPD. We hypothesized that lymphangiogenesis is part of COPD pathogenesis.

Aims and objectives: To investigate the lymphangiogenetic expression in COPD measuring the lymphatic microvessel density (LMVD) and the correlation with the presence of lymphatic invasion (LI), clinical and laboratory parameters.

Methods: Lung surgical specimens from 20 smokers (10 COPD-smokers (30% stage 2 GOLD) and 10 non-COPD smokers) with mean age of 62.6 years (range 38-82) were immunohistochemically stained for D2-40 and LYVE-1. Calculation of LMVD and assessment of LI were performed and correlation with clinical and spirometric data was evaluated.

Results: D2-40 and LYVE-1 were expressed in all specimens presenting higher expression (LMVD) in COPD-smokers (p=0.00). LI was presented in all COPD specimens. D2-40 and LYVE-1 LMVD were associated with the presence of COPD (r=0.20, p<0.01), smoking status (r=1.8, p<0.09), and disease severity (GOLD) (r=0.40).

Conclusions: D2-40 and LYVE-1 being selective lymphatic endothelial markers were highly expressed in COPD specimens in comparison with non-COPD smokers and associated with clinical and spirometric data. Our results reported for the first time the presence of newly formed lymphatic vessels in COPD, thus providing a novel insight in the pathogenesis of COPD including lymphangiogenesis.

PP120 Cigarette smoke-induced lung emphysema in mice is associated with prolyl endoproteasidase, an enzyme involved in collagen breakdown

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There is increasing evidence that the neutrophil chemoattractant proline-glycine-proline (PGP), derived from the breakdown of the extracellular matrix, plays an important role in neutrophil recruitment to the lung. PGP formation is a multistep process involving neutrophils, metalloproteases (MMPs) and prolyl endopeptidase (PE). This cascade of events is now investigated in the development of lung emphysema. Mice were whole body exposed to cigarette smoke for 1 week or 2 weeks. After 1 week, 20 weeks or 8 weeks after smoking cessation animals were sacrificed and bronchoalveolar lavage fluid and lung tissue were collected to analyze neutrophilic airway inflammation, MMP-9 levels, PE activity and PGP levels. Lung tissue degradation was assessed by measuring the mean linear intercept. Additionally, we investigated the effect of the peptide, L-arginine-threonine-arginine
(RTR), that bind to PGP sequences, and the PE inhibitor valproic acid (VPA) on the smoke-induced neutrophil influx in the lung after 1 week smoke exposure. The amount of neutrophils, MMP-9 levels, PE activity and PGP levels were elevated in the lungs of cigarette smoke-exposed mice, while after smoking cessation these parameters were decreased or reduced to normal levels. PE was highly expressed in epithelial and inflammatory cells in lung tissue of cigarette smoke-exposed mice. Moreover, RTR and VPA inhibited the air-estricted neutrophil influx in the lung after 1 week smoke exposure. Together with MMPs, PE may play an important role in the formation of PGP and thus in the pathophysiology of lung emphysema.

This work was performed within the framework of the Dutch Top Institute Pharma Project Ti-103.

PP121
Mononuclear inflammation and alveolar airspace enlargement following targeted deletion of GαqGβ11 in surfactant protein C-positive epithelial cells
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Activation of latent transforming growth factor beta (TGFβ) by the epithelia-restricted αvβ6 integrin is induced by activators of the RhoA signalling pathway and is important in the pathogenesis of lung injury and fibrosis. To establish the role of G-proteins in normal lung development and lung injury, we generated mice with targeted deletion of the α-subunits of Gq11 or G12/13 in Surfactant protein C (SpC)-positive epithelial cells. Lungs were collected 6 and 8 weeks after birth, perfused, fixed by inflation with formalin and processed for immunohistochemical and histochemical analysis.

At 6 weeks, lungs from SpfC-GαqGβ11 knockout mice contained inflammatory infiltrates of primarily mononuclear leukocytes. Inflammation was associated with localised disruption of alveolar architecture and appearance of enlarged alveolar macrophages within alveolar spaces. At 8 weeks, inflammatory foci were more numerous and lung architecture was severely disrupted with multiple abnormally large alveolar spaces detected. In the SpfC-Cre Gαq-Gβ11 lungs, apoptosis was detected in areas of abnormal alveolar architecture containing alveolar macrophages and inflammatory cells but did not co-localise with pro-SpC-positive cells. We detected no abnormal lung phenotype in the SpfC-Cre GαsG12Gβ13 knockout mice at any time point.

These data suggest that a deficiency in Gq11 signalling results in pulmonary inflammation and increased alveolar airspace size. The phenotype is consistent with a role of G-proteins in assessing defects in TGFβ signalling in vivo. Further studies are required to determine whether there are any abnormalities in TGFβ activation in these animals.

PP122
IL-1β drives lung dysfunction and inflammation during viral-induced exacerbations of COPD
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Chronic obstructive pulmonary disease (COPD) is one of the world’s leading diseases predicted to be the 3rd highest cause of death by 2030. Acute exacerbation of COPD can be caused by bacterial and viral infections and is linked to enhanced recruitment of inflammatory cells to the airways, and to increased levels of several inflammatory mediators, such as IL-1β. It remains unknown whether IL-1β is simply an indicator of the inflammation or whether it actively participates in the cellular recruitment and acute lung dysfunction during exacerbations of COPD. We induced COPD in IL-1β-deficient mice by administration of LPS and elastase over 4 weeks; notably, IL-1β did not appear to influence the development of COPD. We then induced an exacerbation of COPD by infecting these mice with Influenza virus. Mice lacking IL-1β showed reduced exacerbation scored by the influx of neutrophils to the airways and by lung dysfunction measured by oxygen saturation and partial pressure of O2 and CO2 in the blood. This was associated with decreased levels of IL-17A (a cytokine leading to the recruitment of neutrophils) by μ and ν T cells. In support of these data, we found that treatment of mice with the IL-1R antagonist, Anakinra (Kineret®), prior to infection provided a comparable level of protection against lung dysfunction. Interestingly, IL-1α partially participated in the virus-induced exacerbation as ν T cell (but not μ) T cell recruitment, IL-17 production and neutrophil recruitment were reduced in IL-1α-deficient mice. These data reveal an important role for IL-1 in virus-induced exacerbations of COPD and highlight the possibility of the use of therapeutic targeting this pathway for treatment.

PP123
Lung CD8+ T cells induce apoptosis of autologous lung target cells in COPD
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Introduction: CD8+ T cells are implicated in COPD pathogenesis, yet whether they induce apoptosis of structural lung cells is unknown. CD8+ T cell cytotoxicity and unced when their NKG2D receptor binds ligands upregulated by stressed cells. In human lung biopsies, expression of an NKG2D ligand, MICA, is associated with emphysema.
Objectives: We hypothesized that lung CD8+ T cells contribute to COPD progression by killing autologous lung cells via interactions between NKG2D and MICA.
Methods: We used lung tissue from clinically-indicated resections for flow cytometry (n = 30) to analyze expression of NKG2D on CD8+ T cells and MICA on CD326+ epithelial cells. Results, as a % of positive cells and mean fluorescent intensity (MFI), were correlated to FEV1, % predicted and radiographic emphysema scores using Spearman statistic. Additionally (n=12), isolated lung CD8+ or CD4+ T cells were co-cultured with the remaining “target” cells for 4 hours, then viability was analyzed by annexin V7-AAD staining.
Results: Co-culture with lung CD8+ T cells, but not CD4+ T cells, significantly decreased target cell viability and this decrease was significantly greater in COPD patients. NKG2D MFI on lung CD8+ T cells was highly correlated with emphysema severity; but not FEV1 % predicted. Expression of MICA on lung CD326+ epithelial cells correlated directly with emphysema severity and inversely with FEV1 % predicted. MICA and NKG2D MFI within individual patients correlated strongly.
Conclusions: These results imply that lung CD8+ T cells, but not CD4+ T cells, can kill autologous lung cells and that increased expression of NKG2D and MICA may be contributing to the pathogenesis of emphysema.

PP124
Cigarette smoke-induced inflammation promotes melanoma cell metastasis in lung parenchyma
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It is only during the last decade that clear evidence has been obtained that inflammation plays a critical role in different stages of tumor development, including initiation, promotion, metastasis and angiogenesis. The increase in evidence that an inflammatory microenvironment is an essential component of all tumors (Paal and Lyden, Nat Rev Cancer, 2009 Apr;9(4):285-93). In the present study, we assessed in vivo the impact of cigarette smoke (CS) on the tumor cell extravasation in lungs after tail vein injection of B16F10 melanoma cells. We first characterized airway inflammation obtained after smoke exposure (reference cigarettes IR4F) for varied time periods (1, 2, 4, 8 and 12 weeks). Smoke exposure was performed 5 days a week. Neutrophils, alveolar macrophages, interstitial macrophages, dendritic cells, T cells and natural killer T (NKT) cells, were characterized in lung tissues of mice exposed to CS and AIR using flow cytometry. In vitro, the direct effect of cigarette smoke extract (CSE) on proliferation of B16F10 melanoma cells was determined for 1 to 5 days. In vivo, mice exposed for 2 weeks to cigarette smoke or air were injected with B16F10 melanoma cells in the tail vein. After 3 weeks, hematoxylin and eosin stained lungs were analyzed for lung metastasis (tumor area/total lung area). An increase of metastasis and implantation site in lungs was observed in CS exposed group. Conceivably, CS constituents significantly promote extravasation of melanoma cells in lung tissues. The mechanism or signaling pathway responsible for this dissemination needs to be further investigated.

PP125
Identification of a steroid-insensitive sub-population of macrophages in COPD lung
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In COPD, alveolar macrophage numbers are elevated and released increased levels of inflammatory mediators but respond poorly to glucocorticosteroids. Identifying the cells from tissue residue of cytokines and separated using Percoll density gradients (A:10-20%, B: 20-30%, C:30-40%, D:40-50%, E:50-60%). Viability and responses to budesonide following stimulation with lipopolysaccharide (LPS) were investigated by measuring CXCL8, TNFα, MIP-2 and IL-10 release by ELISA. Fraction C and B were apoptotic or necrotic, whereas the remaining fractions were >70% viable and used for analysis. Budesonide inhibited LPS-stimulated TNFα release by fraction C smoker macrophages in a concentration-dependent manner (IC50=1±1.1±0.8nM). This inhibition was not seen in COPD macrophages. Fraction C COPD macrophages were significantly less sensitive to budesonide with respect
COPD is a chronic inflammatory disease mainly caused by cigarette smoke (CS) and characterized by infiltration of (activated) inflammatory cells. Airway smooth muscle (ASM) and epithelial cells also contribute to inflammatory cytokine release, smooth muscle contraction, and airway remodeling. Notably, cAMP-elevating β2-agonists and phosphodiesterase inhibitors differentially diminish COPD symptoms. Compartamentalization of cAMP by AKAPs could explain distinct cAMP responses. In human ASM and epithelial cells, CS-induced IL-8 release was decreased by fenoterol, the PKA activator 6-bnz-cAMP, while the Epac activator 8-pCPT-2'-OcAMP showed only slight effects. Addition of PKA-AKAP mimetics to an inhibitor H83 augmented the IL-8 release. Exposure of epithelial cells to CSE reduced barrier function, and redistributed E-cadherin from cell-cell contacts. RII overlay, western blots and RT-qPCR demonstrated expression of AKAP79, AKAP250 and AKAP450. CSE decreased AKAP250, whereas AKAP79 was less affected and AKAP450 even enhanced, indicating disturbance of AKAP functions by CSE. Importantly, similar changes in AKAP expression were found in lung tissues of COPD patients. Our studies provide the first relation between cigarette smoke and the coordination of cAMP signaling by AKAPs. Supported by the Dutch Asthma Foundation and a Rosalind Franklin Fellowship.

**PP129**

**Suppression of antitumor immunity as a potential link between inflammation and cancer in COPD**

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**Background:** COPD is an independent risk factor for lung cancer. Chronic inflammation facilitates tumor development through non immune and immune mechanisms including the penetration of myeloid cells resulting in dysfunction of Ag-presenting cells and dysfunctional cell-mediated antitumor immunity. We hypothesize that chronic systemic inflammatory character of COPD is associated with an expansion of cell populations that suppress antitumor immunity and that these changes are even more evident in COPD with lung cancer (LC).

**Methods:** The percentage of myeloid derived suppressor cells (MDSC) and dendritic cells (DCs) from blood was quantified by flow cytometry in 18 patients with COPD (mean ± SD, FEV1 = 68±14% pred); 17 smokers with normal lung function (SC) (FEV1 = 104±15% pred) and 20 non-smokers (NSC) (FEV1 = 101±20% pred).

**Results:** COPD patients had an increased number of MDSC (median, range: 79.2; 817 cells x μl−1) as compared to NSC (21.1; 338; p<0.002). In addition they showed a reduced percentage of DCs with respect to NSC (10.4; 1.6%; 0.6%; 8%; p<0.02, respectively). To test whether the presence of LC influences these cell populations we compared COPD patients with patients with LC but we did not find any statistically significant result. However, the ratio between MDSC/DC progressively increased in patients with COPD and LC (NSC: 0.6; SM: 1.2; COPD: 2; SM LC: 2.3; COPD LC: 3.3).

**Conclusions:** In COPD patients there is an altered pattern of blood MDSC and DCs suggesting a blunted antitumor immunity in this disease as a potential link between inflammation and cancer. These findings are similar to those evident in patients with LC.

**PP130**

**Oxidative DNA damage in non-CF bronchiectasis: Differences with COPD**

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**Introduction:** Oxidative stress is believed to play an important role in the pathophysiology of chronic inflammatory airway diseases such as chronic obstructive pulmonary disease (COPD) and non CF-bronchiectasis. Activation of immune and inflammatory cells associated with the generation of reactive oxygen and chemical messengers such as tobacco smoking induces a marked production of oxidants.

COPD is an inflammatory lung disease characterized by chronic airflow obstruction, which is not fully reversible and is due to the chronic exposure to cigarette smoke or other ambient pollutants. The disease is associated with a significant increase in mortality and morbidity, and is a leading cause of hospitalization and healthcare costs. The pathogenesis of COPD is complex and involves the interaction of numerous cellular and molecular pathways. One of the key mediators in the inflammatory response in COPD is the Activating Factor (BAFF) which is a member of the tumor necrosis factor (TNF) family and plays a crucial role in the regulation of B-cell development and survival. BAFF binds to three receptors: TNFRSF13A, TNFRSF13B, and TNFRSF17, which are expressed on B cells, activated T cells, and dendritic cells, respectively. BAFF is involved in the recruitment and activation of regulatory T cells (Tregs), which play a critical role in maintaining immune homeostasis and preventing autoimmune diseases.

The paper by Francesca Polverino and colleagues investigates the role of BAFF in the interaction between T regulatory and B cells in chronic obstructive pulmonary disease (COPD). The study found that BAFF expression is increased in COPD patients compared to healthy controls. BAFF expression in B lymphocytes and Tregs was higher in COPD patients, especially in smokers, suggesting a potential role of BAFF in the pathogenesis of COPD.

BAFF expression in B lymphocytes and Tregs from COPD patients was measured using flow cytometry. The results showed a significant increase in BAFF expression in B lymphocytes and Tregs from COPD patients compared to healthy controls. The levels of BAFF expression were higher in smokers and COPD patients than in non-smokers and healthy controls. The increased expression of BAFF in COPD patients suggests a potential role of BAFF in the pathogenesis of COPD.

**Methods:** Peripheral blood mononuclear cells of COPD patients and healthy controls were isolated and stimulated with anti-CD3 and anti-CD28 antibodies. BAFF expression was measured using flow cytometry. The results were analyzed using statistical software.

**Results:** The authors found a significant increase in BAFF expression in B lymphocytes and Tregs from COPD patients compared to healthy controls. BAFF expression was higher in smokers and COPD patients than in non-smokers and healthy controls. The increased expression of BAFF in COPD patients suggests a potential role of BAFF in the pathogenesis of COPD.

**Conclusions:** The study by Francesca Polverino and colleagues provides evidence for the potential role of BAFF in the pathogenesis of COPD. The increased expression of BAFF in B lymphocytes and Tregs suggests that BAFF may contribute to the chronic inflammatory process in COPD. Further studies are needed to investigate the mechanisms by which BAFF contributes to the pathogenesis of COPD and to explore the potential therapeutic targets for the treatment of COPD.
Conclusion:

TLR 9 KO animals and the controls.

Chronic obstructive pulmonary disease (COPD) is characterized by septal tissue inflammatory cell influx changes in the lung. TLR 9 deficiency does cause an increase in smoking, and evidence suggests that innate and specific immune cells are involved. Cigarette smoke-concentration determines dynamics of inflammatory cell infiltration. Results: Bronchoalveolar lavage (BAL) fluid of 7 months old TLR 9-/- and wild type C57BL/6 (WT) was examined for total and differential cells. Total BAL cells, macrophages, and lymphocytes were increased after exposure to 350 ppm CSE for 1 day compared to controls. Total BAL cells were 30% increased in TLR9-/- mice. Differential cell count showed only increased numbers of macrophages. CpG increased TNF-α and IL-6 production by bronchoaveolar lavage- and lung homogenate cells. RNA expression of proinflammatory genes in lung tissue was used to determine mRNA expression of proinflammatory genes TNF-α and MIP-2 by quantitative real-time PCR. Neutrophils were significantly increased after exposure to cigarette smoke-concentrations of 250 mg/m³ for 1 day and 3 days compared to control animals, whereas macrophages and lymphocytes were elevated after exposure to 350 mg/m³ for 3 days. Exposure to concentrations of 500 mg/m³ led to an increase in macrophages only, which was associated with an increased mRNA expression of TNF-α and MIP-2.

The results demonstrate that cigarette smoke-concentration determines the dynamics of inflammatory cell recruitment in an acute COPD mouse model. Female C57BL/6 mice were exposed to cigarette smoke-concentrations of 250, 350, and 500 mg/m³ total particulate matter for 4 hours per day for 1 and 3 days. Animals were sacrificed 24 h after the last exposure. Control animals were kept in a filtered air environment. BAL fluid was obtained to perform differential cell counts and lung tissue was used to determine mRNA expression of proinflammatory genes TNF-α and MIP-2 by quantitative real-time PCR. Neutrophils were significantly increased after exposure to cigarette smoke-concentrations of 250 mg/m³ for 1 day and 3 days compared to control animals, whereas macrophages and lymphocytes were elevated after exposure to 350 mg/m³ for 3 days. Exposure to concentrations of 500 mg/m³ led to an increase in macrophages only, which was associated with an increased mRNA expression of TNF-α and MIP-2.

The results demonstrate that cigarette smoke-concentration determines the dynamics of inflammatory cell recruitment in an acute COPD mouse model. Male and female C57BL/6 mice were exposed to cigarette smoke-concentrations of 250, 350, and 500 mg/m³ total particulate matter for 4 hours per day for 1 and 3 days. Animals were sacrificed 24 h after the last exposure. Control animals were kept in a filtered air environment. BAL fluid was obtained to perform differential cell counts and lung tissue was used to determine mRNA expression of proinflammatory genes TNF-α and MIP-2 by quantitative real-time PCR. Neutrophils were significantly increased after exposure to cigarette smoke-concentrations of 250 mg/m³ for 1 day and 3 days compared to control animals, whereas macrophages and lymphocytes were elevated after exposure to 350 mg/m³ for 3 days. Exposure to concentrations of 500 mg/m³ led to an increase in macrophages only, which was associated with an increased mRNA expression of TNF-α and MIP-2.

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times observed. The levels of proinflammatory cytokines IL-1β, IL-6 and IFN-γ were significantly increased in rats exposed to TS compared to FA animals. Airway obstruction was noted as a significant elevation in central airway resistance (Rn) and tissue damping (G) (small airway and tissue resistance). Rn was increased at 4 weeks, reduced at 6 weeks and significantly elevated at 10 and 12 weeks. G was significantly increased at 4 weeks, followed by a slight decrease that remained significantly elevated through 12 weeks. Significant correlations between IL-1β, IL-6, IFN-γ, TNF-α and degree of tissue damping were noted.

**Conclusions:** Progressive airway obstruction and abnormal inflammatory response to smoke in this rat model of COPD is associated with dysregulated immune responses and impaired physiological lung function. Elucidation of those mechanisms underlying immunologic alteration specific to tobacco smoke in this rat model of COPD could significantly contribute to a better understanding to treat chronic inflammatory lung diseases.

PP136

Chemokine Expression by small sputum macrophages in COPD
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Small sputum macrophages represent highly active cells that increase in the airways in patients with inflammatory disease like chronic obstructive pulmonary disease (COPD). Using macrophage purification and flow cytometry we now show that in COPD these cells account for 85% compared to 13% in control donors. When looking at chemokine expression we found for the small macrophages in COPD an increased transcript and protein levels for CCL2, CCL7, CCL13 and CCL22 with a more than 100-fold increase for CCL13 mRNA. Looking at active smokers without COPD there is a substantial increase of small macrophages to 60% and here chemokine expression is increased as well. In a model of airway inflammation healthy volunteers inhaled 200 μg of lipopolysaccharide (LPS) and this resulted in an increase of small sputum macrophages from 18% to 64%. The pattern of chemokine expression was, however, different with an up-regulation for CCL2, CCL7, CCL13 while CCL11 was down-regulated in the LPS induced small macrophages. These data demonstrate that sputum macrophages in COPD show induction of a specific set of CCL chemokines. Is distinct from which can be induced by LPS.

PP137

MMP8, MMP9 and TIMP1 mRNA & protein expression is upregulated in patients with chronic obstructive pulmonary disease (COPD)
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Matrix metalloproteinases (MMPs) and their tissue inhibitors of (TIMPs) have been implicated in pathogenesis of COPD. Information about their expression locally in the lung is limited and about their association with the risk of recurrent exacerbations in COPD patients has been limited. To determine local/systemic levels of MMPs and TIMPs in COPD patients/control subjects. To evaluate plausible relationship between MMPs/TIMPs and COPD exacerbations. MMP2,8,9 and TIMP-1 mRNA & protein expression were investigated in bronchoalveolar lavage (BAL) cells and fluid in 28 COPD patients and 28 control subjects using qRT-PCR and xMAP technology. In parallel, MMP2,3,7,8,9,10 and TIMP-1 were determined in serum. COPD was diagnosed according to GOLD criteria; number of exacerbations assessed during 2 years follow-up. Mann-Whitney U test/Spemann’s correlation test were used for statistics. Compared with controls, increase of MMP8,9 mRNA and of MMP8,9 protein was detected in COPD BAL cells/fluid; MMP8,9 were increased in patients’ serum, together with MMP1 and MMP7. Of studied TIMPs, TIMP1 and TIMP2 proteins were upregulated in COPD BAL fluid, TIMP3 mRNA in diseased BAL cells; TIMP1 and TIMP4 were increased in serum. Number of COPD exacerbations correlated with serum MMP3 concentration and also with the MMP3/TIMP3-1 ratio. In our COPD cohort, MMP8, MMP9 and TIMP1 were upregulated both locally and systemically. Moreover, serum MMP3 and its ratio to TIMP1-3 correlated with the number of exacerbations in our patients. Studies are required to confirm MMP3 as a marker for assessment/diagnosis of exacerbations. Support: IGAMZCR 10267; PUL 2010/008.

PP138

The role of lipoxin A₄ in the chronic obstructive pulmonary disease
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**Aim:** Chronic obstructive pulmonary disease (COPD) is characterized by persistent inflammatory reaction with a dominance of neutrophil involvement. It is established, that during a healing of acute inflammation, a switching of arachidonic acid (AA) metabolism from leukotriene (LT) to lipid (LX) production occurs. Therefore we hypothesized that in COPD patients the lipoxin production could be insufficient. Hence we measured the content of LXA₄ and LtB4 in induced sputum supernatant in COPD patients and healthy subjects.

**Materials and methods:** 17 COPD patients and 7 healthy persons were studied. The age and gender ratios were similar in both groups. Sputum induction was performed according to the ERS protocol. LXA₄ and LtB4 content in sputum supernatant was assessed by ELISA.

**Results:** COPD patients had decreased concentration of LXA₄ in induced sputum compared to healthy persons (0,514 ng/ml and 1,310 ng/ml, respectively, p=0,00784). LtB4 content in induced sputum did not significantly differ between COPD group and healthy persons group (3,551 ng/ml and 3,754 ng/ml, respectively). The ratio LtxB₄/LXA₄ in COPD patients was three times higher compared to healthy persons (ie. 9,816 ng/ml and 3,425 ng/ml; p=0,00982).

**Conclusions:** We concluded that the chronic obstructive lung disease is characterized by suppressed production of lipoxins. This insufficiency may be responsible for a persistence of neutrophil inflammation in airways.

PP140

Chronification of pulmonary inflammation in a nanoparticle exposure model
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While inflammatory responses to pulmonary deposited carbon nanoparticles (NP) are of transient nature, fibroblasts and macrophages may play a key role in the transition from acute to chronic inflammation.

We analyzed the inflammatory responses provoked by spherical carbon NP (CNP) and nanotubes (CNT) up to day90 after intratracheal instillation in mice. We propose that our detailed comparisons could help to understand underlying mechanisms of non-resolving, chronic inflammation.

Instillation of 50ng CNP or CNT caused acute pulmonary inflammation in mice, characterized by an influx of 200-240×10³E3 neutrophilic leukocytes, recovered byavage (BAL) respectively. A reaction resolved by 75% at day7 and completely till day90 after CNP exposure, but only by 40% at day7 with 46×10³E3 neutrophils remaining at day90 for CNT treatment. Chronification of non-resolved inflammation upon CNT treatment was further indicated by till day90 increasing lymphocyte and macrophage counts, accompanied by multinucleated macrophages, a sign for impaired particle phagocytosis. Comparing fractions of particle laden BAL macrophages at day7, revealed for CNT 20% but over 60% for CNP exposed mice. At this stage immunohistochemistry identified highest expression of Gal-C3m, a marker for alternatively activated macrophages with proinflammatory activity, in particle-free but not in particle-laden BAL macrophages.

These data suggests that newly recruited macrophages, rather than unsuccessful phagocytosing, resident cells might contribute to conditions of chronic inflammatory and fibrotic diseases.

PP141

The relationship of CD4+/CD8+ ratios and Toll like receptor-2 expression with COPD and smoking
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**Aim:** Native immune system activates acquired immunity by Toll Like Receptors (TLR). There may be some alterations in T cell profile and TLR expression in peripheral blood monocytes of COPD patients. We aimed to evaluate the utilization of the ratio of CD4, CD8 T cells and TLR-2 expression as a marker of lung pathology as well as their relationship between pulmonary function tests in COPD patients and smokers.

**Method:** Forty stable COPD patients admitted to our university’s outpatient clinic and 40 volunteers were included in the study. The study population was evaluated in 4 groups according to their smoking status. CD4+, CD8+ T cells and monocyte TLR-2 expression was measured by flow cytometry in patients and control groups. Spironometry was performed in the whole study population except for nonsmoker control group.

**Results:** TLR-2 expressions investigated in CD14+ cells were found %5±6.2% in Group 1 (nonsmoker COPD), %6.5±6.3% in Group 2 (smoker COPD), %6.4±4.4% in Group 3 (healthy smoker) and %5.2±2.5% in Group 4 (healthy nonsmoker), any difference was not observed between the groups. CD4+, CD8+ T cells and CD4+/CD8+ ratios were not found to be different between the groups. CD4+ T cells and FeV_, FeV/FcV also had a positive correlation (r=0.311, p=0.01; r=0.293, p=0.023, respectively). CD4+/CD8+ ratios and FeV/FcV also showed positive correlation (r=0.295, p=0.022). Smoking amount and CD4+/CD8+ ratios had a negative correlation (r= -0.274, p=0.034).

928s
Chronic obstructive pulmonary disease (COPD) is characterized by an abnormal inflammatory response to tobacco smoke. COPD patients frequently present exacerbation episodes (ECOPD) involving increases of the inflammation, these exacerbations are mainly due to bacterial infections. Aims: Evaluate the functionality of TLRs and NLRs in peripheral blood cells of COPD patients both during stable and exacerbated disease. Methods: 48 individuals were included in the study: 11 healthy controls, 8 healthy smokers, 13 stable COPD and 9 exacerbated COPD seven of which were reanalyzed 3 months later at stability phase. PBMCs were isolated and stimulated with agonists of TLR4, TLR5, NOD1 and NOD2. The level of IL-1β, IL-6 and TNF-α produced in the supernatant was assessed. Results: PBMCs from patients with ECOPD produced lower amounts of IL-6 in response to TLR4, TLR5, NOD1 and NOD2 and levels of IL-1β in response to NOD1 and NOD2. The level of IL-1β and TNF-α synthesised exponenlately and in response to TLR5 and TLR9 did not differ among the groups. In patients with stable COPD the severity of an immune interaction and the capacity to synthesize IL-1β in response to TLR-4, TLR5 and NOD1 correlate. Conclusions: The functionality of the TLRs and NLRs and the ability to response bacterial stimuli is different in patients with stable COPD and exacerbated COPD.

Evaluation of morpho-functional changes in airways of young cigarette smokers

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We assumed that even in asymptomatic young smokers, with relatively short smoking duration and normal lung function, induced sputum could be found some changes indicative for early inflammatory process. Aims: The aim of this study was to evaluate morpho-functional changes in airways of young cigarette smokers.

Method: We enrolled 23 ± 3 years old 12 non-allergic smokers (1.59 ± 0.67 pack-years) and 7 healthy non-smoking volunteers. Lung function measurements, sputum induction and sputum cell analysis were performed.

Results: Demographic data for both study groups did not differ significantly. Non-smokers and smokers had normal lung function indices. In smokers induced sputum contained statistically significantly (p=0.026) increased relative count of eosinophils 0.923 (0.355-1.753) % compared with non-smokers 0.069 (0.046-0.550) %. We also found significant reduction of absolute (r =0.402; p=0.0872) and relative (r=0.482; p=0.037) count of bronchial epithelial cells in induced sputum that correlated to number of smoked pack-years. A trend towards statistical significance showed the correlation between smoked pack-years and the relative number of macrophages in induced sputum (r =0.402; p=0.0872). A trend towards statistical significance was also found in correlation between smoked pack-years and diminished FEV1% of predicted (r =-0.463; p=0.046). Conclusion: In this study we showed that even smokers with short duration of the smoking habit have already initial signs of inflammation with eosinophil involvement.

Evaluation of morpho-functional changes in airways of young cigarette smokers

PPI43

Elastase is inducing irreversible emphysema correlated with impaired pulmonary function in mice

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Rationale: Chronic obstructive pulmonary disease (COPD) is characterized among others by development of emphysema, which is known to occur as a result of imbalance of proteases and antiproteases. A variety of enzymes, like neutrophil elastase and matrix metalloproteinase 12 (MMP-12), are capable of de-stressing parenchymal tissue, causing loss of alveolar and airway enlargement in the lung. We showed that a single application of porcine pancreatic elastase (PEE) causes a severe emphysema-like phenotype in C57BL/6 mice.

Methods: We instilled mice oropharyngeally with PPE. Animals in control groups received a comparable volume of PBS. Measurements of lung function parameters using Buvox and FlexiVent systems and histological analysis of lung tissue on several time points until 160 days after application were performed to follow the development of an emphysema phenotype.

Results: A continuous decline in lung function parameters like compliance, forced expiratory volume in 100ms (FEV1) or the Tiffenau index (FEV1/FVC) was determined in these experiments. Airway enlargement was reflected in increase of total lung capacity (TLC), vital capacity (VC) or functional residual capacity (FRC). These developments played along with the histological analysis of lung tissue from these mice, which presented progressing loss of alveolar septae and the resulting airway enlargement from day 2 after application of porcine pancreatic elastase until day 160.

Conclusion: Severe emphysema developed after a single application of porcine pancreatic elastase, distinguished by ongoing damage of lung tissue which exactly matched the resulting impairment of lung function parameters in this emphysema mouse model.

PP145

Effect of cigarette smoke extract or TGF-β1 on hyaluronan production and hyaluronan modulating enzymes in primary murine lung fibroblasts

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Hyaluronan (HA) is a component of the extracellular matrix and low molecular weight (LMW) HA fragments have pro-inflammatory capacities. Exposing mice to cigarette smoke (CS) for 1 or 6 months results in enhanced deposition of LMW HA in lung parenchyma and airway walls and in altered expression of HA syntheses and hyaluronidases (Bracke et al., Am J Respir Cell Mol Biol. 2010;42(6):753-61). To pinpoint a source of HA, we studied HA-production and expression of HA modulating enzymes in primary murine pulmonary fibroblasts stimulated with cigarette smoke extract (CSE) or TGF-β1.

Fibroblasts were isolated from lungs of C57BL/6 mice and cultured in vitro. At passage 6, cells were stimulated for 24 or 48 h with 1 or 10% CSE or 1ng/ml TGF-β1. mRNA expression of HA syntheses (Has1, Has2, Has3) and hyaluronidases (Hyal1, Hyal2) was evaluated by RT-PCR. HA production was measured in supernatant by ELISA.

In vitro stimulation of pulmonary fibroblasts with CSE significantly decreased the mRNA expression of Has1 (synthesizing high molecular weight (HMW) HA) and significantly increased the expression of Hyal2 (degrading HMW HA fragments). Stimulation with TGF-β1 resulted in significantly increased mRNA expression of Has2 (synthesizing HMW HA). Accordingly, HA-levels in the fibroblast supernatant decreased significantly upon 48h stimulation with CSE, while they were significantly increased upon 24h or 48h stimulation with TGF-β1. Decreased Has1 and increased Hyal2 in CSE-stimulated fibroblasts suggests reduced synthesis and enhanced breakdown of HMW HA. This may contribute to the accumulation of LMW HA fragments, observed in CS-exposed mice.
EMT has been implicated as an important mechanism in the pathogenesis of fibrotic airway diseases such as Obliterative Bronchiolitis (OB). TGF-β1 has been shown to drive EMT both in vitro & in vivo. Previous observations have shown that inflammatory stimuli such as TNFα can accentuate TGF-β1 driven EMT in Primary bronchial epithelial cells (PBEC). We hypothesize that TAK-1 may act as a convergence point for this signalling pathway.

PBEC were treated with TGF-β1 (10ng/ml) or TNFα (20ng/ml) and TAK-1 phosphorylation assessed. TAK-1 function was blocked by specific inhibition or siRNA knockdown and the effect on EMT assessed. Tissue sections from control and post transplant patients with OB were analyzed for TAK-1 phosphorylation. TAK-1 is phosphorylated in response to TGF-β1 (+161% over control) and TNFα (+145%) with an accentuation (+516%) and nuclear translocation upon cotreatment (n=3). Furthermore strong phosphorylation and nuclear localization of TAK-1 was also observed in OB tissue. Selective inhibition of TAK-1 phosphorylation and nuclear localization significantly reduces the TGF-β1 driven EMT [loss of E-cadherin (39%), gain of Vimentin (28%) and Fibronectin (87%) p<0.05 (n=6)]. These findings were validated via siRNA knockdown of TAK1 (n=3). TAK1 is an important signalling molecule for the accentuation of EMT in lung epithelium identifying TAK-1 inhibition as a potential new therapeutic target in airway disease.

Nitrergic mechanisms may play a role in the control of airway inflammation in asthmatics and COPD patients. Previous studies using NO donors have shown that NO can modulate the release of cytokines by matured DCs. We have shown that activated macrophages can accentuate TGF-β1 driven EMT of cells in a concentration-dependent manner with 300μg/ml showing ~80% inhibition (control: 31.1±5.0 to 151.3±54.0 μg/ml DEP: 619±180 RFU, n=29), with MDM being 70% viable at this concentration, with no difference in response between the different subject groups. These data show that DEP impair macrophage phagocytosis and promote chemokine release. These data suggest that DEP may lead to reduced clearance of debris and pathogens from airways and promote COPD exacerbations.

Interleukin 1α is a key epithelial alarm that promotes fibroblast activation Monika Suwara1, Lee Borthwick1, Jelena Mann1, Stuart Farrow2, Derek Mann1, Andrew Fisher1.1
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2Glasco Smith Kline R&D, Immunology Biology Group, Stevenage, GB

Inhalation of inhaled particulates is a major contributor to air pollution and when inhaled become tarred to the lung epithelium. The interaction between DEP and bacteria/endotoxin is numerous in the distal airways but does not appear to affect the number of mast cells. We have described a novel mechanism where NO might play a significant role in the modulation of LPS activation cascades, NO can play different and important roles in DC maturation. Human DCs are underneath epithelial barrier and continuously influenced by the antigens and redox state. We are interested in the role that reactive oxygen species such as nitric oxide (NO) play in DC maturation. Human DC were stimulated with different concentrations of LPS. NO donors and inhibitors were achieved. DC-maturation markers, a panel Th1/Th2/Th17 cytokines and proliferation assays were analyzed. Our results have shown that NO is able to change the pattern of the release of cytokines by LPS matured DC which was dependent on the concentration, as well as in the time point that NO was added to the cells during the maturation. IL-10 and TNFα were released in a dose dependent manner while the release of IL-12 was inhibited. If NO is added before maturation by LPS an inhibition of IL-12 and IL-10 was observed. Interestingly, NO strengthen the role of IL-23, IL-1b and IL-6. Functionally, in spite of the fact co-stimulation of NO with LPS did not modify allo-presenting properties of DCs, NO treated DCs before maturation was able to induce a Th17 polarization in a mixed lymphocyte reaction. NO can play different and important role modulating the LPS activation cascades, depending on the concentration or time point used. Interestingly, NO strongly inhibits the activity of DCs to release IL-12, but strengthen the release of other cytokines such as IL-23 and IL-1b which are involved in a Th17 polarization.

We have described a novel mechanism where NO might play a significant role modulating the release of IL-17, which might be a key element in the pathogenesis of lung diseases such as in asthma or COPD.

Inflammatory cells in the proximal and distal airways: Effects of steroids
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Rationale: Patients with COPD may be prescribed inhaled steroids but it is not clear if this reduces inflammatory cells in either the proximal or distal airways.

Methods: Matched tissue from proximal and distal airways of 28 patients undergoing a lobectomy was fixed in acetone, processed into GMA and inflammatory cells enumerated by immunohistochemistry.

Results: Twelve patients had no evidence of airways obstruction (FEV1/FVC = 0.77±0.03), 10 had mild/moderate COPD (FEV1/FVC = 0.59±0.02) but were not on steroids. Six patients had COPD (FEV1/FVC = 0.39±0.03) and had been prescribed inhaled steroids. There was no difference in age, lung function or smoking histories of the COPD groups. Mast cell numbers were significantly higher in the distal airways in all the groups compared to the proximal airways. Neither COPD or inhaled steroids altered mast cell number in the proximal airways but there was a reduction in the mast cells in the distal airways in patients prescribed inhaled steroids (P<0.05 compared to both non-COPD and non-stEROID groups). Median (IQR) values/mm2 were 52.7 (37.3-61.8) for patients with no airways obstruction, 68.8 (37.5-89.9) in patients with COPD but not taking steroids and 23.6 (16.2-28.6) in the steroid group. Macrophages and neutrophils were more numerous in the distal airways but numbers were not affected by COPD or use of inhaled steroids. T cells were more evenly distributed between the proximal and distal compartments but again were unaffected by either COPD or steroids.

Conclusions: Prescribing inhaled steroids in mild/moderate COPD does not affect the number of any mast inflammatory cells in the lung but does not appear to affect the number of the different inflammatory cells in either the proximal or distal airways.

Classically activated macrophages (CAMΦ) accentuate TGF-β1 driven epithelial to mesenchymal transition (EMT) via secretion of TNFα
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Obliterative Bronchiolitis (OB) is characterised by fibrotic obliteration of small airways adversely affecting survival after lung transplantation. In-vitro and in-vivo primary bronchial epithelial cells (PBEC) from the transplanted lung have been shown to undergo EMT and this may contribute to the development of OB. We have shown that activated macrophages can accentuate TGF-β1 driven EMT.
Macrophages demonstrate remarkable plasticity and change their physiology in response to the microenvironment. We hypothesised that this effect on EMT is limited to CAMφ and that their secretory products may be a target for limiting inflammatory accentuation of EMT. THP-1 cells were differentiated to CAMφ or alternatively macrophages (AAMφ) and stimulated with clinical isolates of Pseudomonas aeruginosa (PA). Cytokine secretion and their effect on TGF-β1-driven EMT were assessed. The effect of blocking TNFα secreted from activated THP-1 cells was also assessed. CAMφ released more TNFα (8.4-fold) and IL-1β (8.1-fold) than AAMφ in response to PA (p < 0.05 n=6). Conditioned media from CAMφ, but not AAMφ, dramatically accentuated TGF-β1-driven EMT (p < 0.05 n=6). Blocking TNFα in conditioned media significantly inhibits the decrease in E-cadherin (39% ± 4%) and the increase in vimentin (59% ± 18%) and fibronectin (72% ± 14%) expression (p < 0.05 n=5). The secretory products of CAMφ, but not AAMφ, significantly accentuate TGF-β1 driven EMT. TNFα appears to be a major constituent of this accentuation raising the possibility that TNFα targets therapies or modulation of macrophage phenotype may inhibit the inflammatory accentuation of EMT in the airway.

**PP153**

Heme-oxygenase (HO)-1 inhibits TNF-α induced CXCL10 secretion by airway smooth muscle cells.

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**Background and purpose:** CXCL10 induces mast cell migration towards airway smooth muscle bundles in asthma. In blood mononuclear cells, induction of heme oxygenase (HO)-1 inhibited pro-inflammatory cytokine secretion. Dimethyl-fumarate (DMF), which is clinically used as an anti-inflammatory medication, induced HO-1 and thereby inhibited proliferation in airway smooth muscle cells (ASMC).

**Experimental approach:** Here we assessed the anti-inflammatory effect of DMF on TNF-α induced CXCL10 secretion in human primary ASMC and the involvement of HO-1 and mitogen activated protein kinases (MAPK). ASMC were pre-incubated with DMF and/or glutathione ethylester (GSH-OEt), SB203580, or the HO-1 inducers hemin, or cobalt-protoporphyrin (CoPP) 1 hour before stimulation with TNF-α (10 ng/ml).

**Key results:** TNF-α induced secretion of CXCL10, which was inhibited by DMF as well as by the HO-1 inducers, hemin, or CoPP. Interestingly, DMF amplified the TNF-α induced phosphorylation of p38 MAPK and thereby induced the expression of HO-1. Inhibition of p38 MAPK by SB203580 reduced DMF-induced HO-1. Importantly, GSH-OEt supplementation: (i) abrogated the inhibitory effect of DMF on TNF-α induced CXCL10 secretion, (ii) counteracted DMF-induced HO-1 expression, and (iii) p38 MAPK activation.

**Conclusion and implications:** Our data indicate that DMF inhibits TNF-α induced CXCL10 by altering intracellular GSH, leading to activation of p38 MAPK and subsequent synthesis of HO-1 in ASMC. Thus, DMF might help to reduce airway inflammation in asthma.

**PP154**

Elevated chitinase proteins in subjects with airway inflammation

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Chitin is a tough structural polysaccharide found in crustaceans, insects, fungi & parasites. Although absent in humans, we express chitinases capable of degrading chitin, of which chitosidase and the chitinase-like protein YKL-40 have been suggested to be a major constituent of this accentuation.

Our aim was to further examine chitosidase and YKL-40 as potential biomarkers of airway inflammation in subjects with asthma & COPD. Blood was collected from well-characterised subjects with asthma (mild & severe) & COPD, taking part in BIOAIR, a European multicentre study. Patient characteristics are shown in table below. Serum chitosidase activity and YKL-40 levels were analysed in a subset of these subjects and compared with results obtained in 66 healthy volunteers.

<table>
<thead>
<tr>
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<th>Mild Asthma</th>
<th>Severe Asthma</th>
<th>COPD</th>
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<tbody>
<tr>
<td>Number of Subjects</td>
<td>76</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42±6.1</td>
<td>50±6.3</td>
<td>61±1.0</td>
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<td>FEV1 (% pred)</td>
<td>88±7.2</td>
<td>70±4.2</td>
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<td>Inhaled corticosteroids (µg beclomethasone eq.)</td>
<td>16±2.29</td>
<td>206±6.94</td>
<td>104±1.60</td>
</tr>
<tr>
<td>Oral corticosteroids (µg beclomethasone eq.)</td>
<td>14±2.61</td>
<td>12±1.3</td>
<td>14±1.3</td>
</tr>
<tr>
<td>Long acting β-agonists (% of study group)</td>
<td>68.4%</td>
<td>94.6%</td>
<td>81.3%</td>
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<tr>
<td>Serum C-reactive proteins (mg/L)</td>
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<td>6.1±0.9</td>
<td>5.9±0.7</td>
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<tr>
<td>SGRQ score</td>
<td>20.9±16.6</td>
<td>42.9±18.6</td>
<td>49±15.1</td>
</tr>
</tbody>
</table>

As shown in the figure below, serum chitosidase activity (A) and YKL-40 levels (B) were significantly elevated in subjects with asthma and COPD, compared to healthy volunteers. Both parameters were greatest in patients with COPD.

The current findings confirm that YKL-40 and chitosidase are useful biomarkers of airway inflammation but also demonstrate that the mechanism underlying increased chitinase expression is not exclusive to asthmatic airway inflammation.

**PP155**

Cigarette smoke dysregulates pro-inflammatory cytokine release from airway epithelial cells and macrophages.

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Chronic obstructive pulmonary disease (COPD) is characterised by repeated bacterial exacerbations which accelerate lung function decline and increase morbidity and mortality. Chronic bacterial colonisation may contribute to airway inflammation and promote disease progression. Cigarette smoke has been shown to alter responses to LPS. We hypothesised that cigarette smoke would suppress the innate immune responses of airway epithelial cells and macrophages to Haemophilus influenzae (H. influenzae) favouring persistence. Primary bronchial epithelial cells (PBEC), alveolar macrophages and a macrophage-like cell line (THP-1) were incubated with cigarette smoke extract (CSE) and stimulated with clinical isolates of H. Cell viability, proliferation and pro-inflammatory cytokine secretion were assessed. CSE concentrations >5% inhibited PBEC proliferation (p < 0.05 n=9). IL-8 release from PBEC was increased in response to HI (p < 0.05 n=3) and this was accentuated by CSE (p < 0.05 n=6). However, treatment with CSE alone had no effect on IL-8 secretion (p > 0.05 n=6). HI treatment increased secretion of IL-8, TNFs and IL-1β from macrophages (p < 0.05 n=3). Co-treatment with HI + CSE increased IL-8 secretion (61%) but reduced TNFs (40%) and IL-1β (24%) secretion compared to HI alone (p < 0.05 n=3). CSE concentrations ≤10% had no significant effect on cell viability.

CSE alters epithelial cell and macrophage responses to bacterial pathogens by promoting release of the neutrophil chemokine IL-8 and suppressing TNFs and IL-1β. This dysregulation may promote continued neutrophil inflammation in the airway whilst insufficiently clearing pathogens and could be an important mechanism in COPD.

**PP156**

Biomedical nanoparticles reduce antigen processing capacity and specific CD4+ T cell stimulation of human dendritic cells

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During particle-cell interaction DC may functionally be affected by nanoparticles (NP) resulting in altered immune responses. The aim of this study is to understand how polyvinylalcohol coated super-paramagnetic iron oxide NP (PVA-SPIPSONs) interact with DC and influence their phenotype and function.

Human blood monocyte-derived DC were treated during 12h with PVA-SPIPSONs imaged by confocal and electron microscopy. Expression of markers of differentiation and activation and the capacity of DCs for antigen-uptake, -processing, and -presentation were studied using flow cytometry and an autologous CD4+ T cell stimulation assay. Cytokine release was measured in MDDC-T cell co-cultures using a multiplex assay.
Primary human type II cells were extracted from patients undergoing lung resection for cancer (n=4). Cells were incubated with VEGF from day 2 to 3 and from day 5 to 6. Gene expression was determined by macroarray analysis and Q-PCR was used to validate the change in type I and II cell markers. Transdifferentiation was associated with significant changes in 417 genes from day 2 to 3, and 935 genes from day 2 to day 6 (1.5+ fold change, p=0.001). VEGF had a dose-dependent effect upon gene expression at day 3 altering 167 genes at ng/ml and 601 genes at 10ng/ml. By day 6 VEGF altered 183 genes at 1ng/ml and 1400 genes at 10ng/ml but the fold changes were small (1.2-2.9 fold). Functional analysis identified that VEGF at day 3 mainly influence cellular development and proliferation processes. By day 6, VEGF also influenced cell metabolism. Only 297 genes were similarly altered at day 3 and day 6 by VEGF 10 ng/ml. Although transdifferentiation was associated with up-regulation of RAGE, Aquaporin V and down regulation of SP-C, VEGF did not affect transdifferentiation markers. Transdifferentiation involves rapid alterations in the mRNA profile of human ATII cells. VEGF influences the expression of genes involved in cellular differentiation and proliferation upon both type II and type I like cells. These data demonstrate that VEGF may have a trophic effect upon type I like cells as well as type II cells at physiologically relevant levels.

Endothelin (ET) receptor blockers have been administered in patients with pulmonary Langerhans’ cell histiocytosis (PLCH) and concomitant pulmonary hyper-tension. The effects of the endothelin receptor type B (ET-B) blocker bosentan on the lung changes of PLCH has yet to be established. We studied the expression of ET receptor A and B in PLCH and investigated the functional significance in vitro. ETAR and ETBR expression was studied in 25 formalin/paraffin-embedded PLCH biopsies. For in vitro analysis, we used the murine LC-like cell line XSS2 and freshly prepared murine and human LCs. Target expression was determined by RT-PCR, cell viability by colorimetric assay, ETAR and TNF-α and IL-12 expression by enzyme-linked immunosorbent assays, cell migration with 48-well Boyden chambers, and ET-1 induced cytosolic calcium mobilization by cell life imaging. Immunohistochemistry revealed expression of ETAR and ETBR in PLCH. In vitro, the expression of the ET system was proven in murine LCs (ETAR+, ETBR+), in human LCs (ETAR+) and in XSS2 cells (ETAR+). Treatment of XSS2 cells with ET receptor blocker revealed impaired cell viability. Migration analysis showed ET-1 dependent migration of LC-like cells, inhibitable by bosentan and the selective ETAR antagonist BQ123. Life cell imaging confirmed ET-1 induced calcium influx. Cytokine monitoring in XSS2 supernatants showed decreased TNF-α levels after bosentan coinubcation. This study reveals unique expression patterns of the endothelin system in PLCH and in murine and human LCs with antiproliferative, antimigratory and antiinflammatory properties of ET receptor blockers in vitro. ET-1 was for the first time found to induce migration of LC-like dendritic cells.

Expression of TLR9 in mouse and human lung and its role in inflammation in chicken barn air exposure

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Workers exposed to intensive animal housing facility air show signs of lung dysfunction. These respiratory symptoms are often associated with endotoxin, but gram negative bacteria may constitute only a small portion of the microorganisms present, whereas unmethylated DNA can be found in all bacteria, some viruses, and mould. Immune responses to this unmethylated DNA are mediated through the Toll-like receptor 9 (TLR9). Therefore we sought to determine the expression pattern of TLR9 receptor in mouse and human lung, and if immune response to barn air exposure would be altered in a TLR9-deficient mouse model. Using immunohistochemistry, immuno-electron microscopy and in situ hybridization we show expression of TLR9 in whole lung tissue of mice and humans in bronchial epithelium, vascular endothelium, alveolar septal cells and alveolar macrophages. For the exposure study C57BL/6 and TLR9-deficient mice were housed in chicken barn air for 8 hours/day for 1, 5, or 20 days. Examination of bronchiolar lavage and serum showed reduced TNF-α levels in TLR9-deficient mice in serum and lung lavage fluids after 5 days (p<0.05) and somewhat reduced at 20 days of exposure (p=0.14), while IFN-γ was also reduced at 5 days in both (p<0.06) and remained reduced after 20 days (p=0.05). A reduction in neutrophils at 20 days was also seen in exposed TLR9-deficient mice (p<0.05) at 20 days as assessed by myeloperoxidase. Our data shows similar expression patterns of TLR9 in mouse and human lungs, and that barn dust DNA, through the TLR9 receptor, may contribute to inflammation induced following exposure to chicken barn air. 

Anti-inflammatory effect of a synthetic pulmonary surfactant containing recombinant human surfactant protein C (SP-C) on lipopolysaccharide-stimulated alveolar macrophages

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Pulmonary surfactant prevents alveolar collapse and protects the lung from infection and inflammation. The aim of this study was to evaluate the effect of a synthetic surfactant, composed of dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoylphosphatidylglycerol (POPG), palmitic acid (PA), and SP-C, on alveolar macrophage activation. We analyzed TNF-α and INOS mRNA and protein levels, as well as phosphorylation of MAPKs, IkBα, and Akt on mouse alveolar macrophages stimulated by bacterial lipopolysaccharide (LPS). We found that all LPS-induced inflammatory markers were inhibited by synthetic surfactant. This anti-inflammatory action is reduced when surfactant vesicles are endocytosed by macrophages, indicating that LPS signaling inhibition might be due to the blockage of LPS binding to its cellular receptor. Antagonism of synthetic surfactant to LPS action is mainly due to the lipid component, whereas SP-C decreases only LPS-induced gene expression. We found that synsurf inhibited LPS-induced TNF-α release, whereas vesicles without POPG have no inhibitory effects. Presence of PA in DPPC/POPG vesicles increases their inhibitory action by inducing ordered/disordered phase coexistence as determined by fluorescence microscopy of giant unilamellar vesicles. Segregation and enrichment of POPG in disordered domains favors the binding of DPPC/POPG/PA vesicles to receptors of the α7A, diminishing LPS signaling. We conclude that the lipid component of SP-C-based synthetic surfactant has an anti-inflammatory action on alveolar macrophages, which reinforces its use in inflammatory lung diseases.
PP162
Investigation of the viral-induced Toll-like receptors axis in bone-marrow mesenchymal stem cells (BM-MSCs) of patients with chronic lung disorders
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Introduction:
Over or under-exuberant Toll like receptors (TLRs) signaling can be deleterious to the host leading to the pathogenesis of chronic inflammatory diseases.
Aim: To investigate molecular characteristics regarding innate immunity involvement in BM-MSCs in patients with COPD in comparison with patients with idiopathic pulmonary fibrosis and autoimmune fibrosis.
Methods: BM-MSCs were studied in 10 COPD patients, 20 patients with pulmonary fibrosis, a idiopathic pulmonary fibrosis (IPF) and b rheumatoid arthritis associated pulmonary fibrosis (RA-UIP) and 10 healthy controls. We evaluated the mRNA expression of the axis of viral induced TLRs in BM-MSCs (passage 2) using quantitative RT-PCR.
Results:
A significant decreased expression in TLR-3 was revealed in both COPD and fibrotic patients compared to healthy individuals (0.5±0.18 versus 0.19±0.12 respectively). A significant increased expression was detected in TLR-3 mRNA levels in COPD in comparison with fibrotic patients (0.51±0.18 versus 0.19±0.12, p=0.002, respectively). In addition, we revealed a significant decreased expression in TLR-8 and TLR-9 in COPD patients compared to healthy subjects (0.04±0.02 versus 0.78±0.3± p=0.001 and 0.2±0.06 versus 0.56±0.6, p=0.001, respectively). A significant decreased expression was measured in TLR-8 in fibrotic patients compared to healthy individuals (14±2.9 versus 7±8 ± 3.5, p=0.02), however, TLR-9 mRNA levels were decreased in fibrotic patients compared with healthy controls (55±8.2± versus 20±5.4, p=0.002).
Conclusion: The aforementioned data may suggest a pathogenetic role of viral induced TLRs in both pulmonary fibrosis and COPD.

PP163
The effect of endothelin-1 on human basophil function in vitro
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Introduction: Endothelin-1 (ET-1) has proinflammatory properties and contributes to allergic late-phase responses. As basophils play a key role in allergic rhinitis or asthma, we investigated the effect of ET-1 on basophils.
Methods: Cells were isolated from venous blood of healthy donors via magnetic cell sorting. Cells were stimulated with 10-7M ET-1 for 15min. To show ETA or ETB receptor expression RT-PCR was performed. The chemotactic effects of EtOH on alveolar macrophage (ETAR) were determined using modified Boyden chambers (positive control MCP-1 10-8M). To explore ET-1 signalling, cells were preincubated with BQ-123 10-5-10-9M or BQ-788 10-5-10-9M. Migration depth was quantified microscopically. Histamine release upon ET-1 (10-8-10-10M) and upon additional stimulation with the secretagogue FMLP 10-9M was determined by ELISA.
Results:
The RT-PCR revealed basophils to express both, ETAR and ETBR. ET-1 (10-8-10-10M) further proved to be a strong chemotactic for human basophils (p<0.0001). Both basophils express both receptors, only the ETAR antagonist BQ-123 10-5-10-12M significantly blocked migration towards ET-1 (10-8M). Furthermore, the histamine release was increased by 2.46 to 2.6 fold after ET-1 stimulation (10-7-10-9M). Interestingly, only the evoking of histamine release by additional stimulation with FMLP 10-9M resulted in a dose dependent effect of ET-1, showing ET-1 (10-10M) to be most effective.
Conclusion: Our observations reveal for the first time that basophils express ETAR and ETBR and ET-1 induces histamine release and basophil migration, which seems ETAR dependent. Considering the fact that ET-1 is involved in the mechanisms of airway inflammation, targeting ET-1 by receptor antagonists may be a new option in the treatment of allergic airway disease.

PP164
The role of alpha-1 antipiryn in regulation of CD14 expression and soluble CD14 levels in human monocytes in vitro
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Introduction: The recognition of bacterial lipopolysaccharide (LPS) is principally mediated by either membrane-bound or soluble form of the glycoprotein CD14. Recent findings indicate that a1-antipiryn (AAT), may not only afford protection against proteases but may also neutralize microbial activities and affect regulation of innate immunity responsible for lung protection. Aim of the study: To investigate influence of AAT on monocytes activity in vitro through regulation of CD14 secretion and expression.
Methods: Human monocytes culture supernatants soluble CD14 and TNFα levels were analysed using ELISA kit. CD14 expression was analysed by flow cytometry.
Results: We find that a short-term (up to 2h) monocyte exposure to AAT induced expression of CD14 and secretion of soluble CD14. It helps monocytes in neutralization of LPS. Longer term (18h) monocytes incubation with AAT decreases expression of CD14 and enhances soluble CD14 secretion, thus monocytes are protected from hyporesponsiveness of bacterial endotoxin. In parallel, a short-term monocytes incubation with AAT, but longer term inhibits LPS induced TNFα release, that shows immunomodulating capacity of AAT. Probably a rapid increase in AAT concentrations during various inflammatory and infectious conditions may enhance monocyte responses to endotoxin and subsequently accelerate resolution of the inflammatory reaction.
Conclusions: These findings provide evidence that AAT is an important regulator of CD14 expression in monocytes and suggest that AAT may be involved in LPS neutralization and prevention of over-activation of monocytes in vivo, that is important mechanism in development of COPD.

PP165
Biomarkers in interstitial lung diseases
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Chronic eosinophilic allergic alveolitis (EAA) and idiopathic pulmonary fibrosis (IPF) both cause lung fibrosis. The aim of our study was to investigate possible use of proinflammatory chemokines (interleukin (IL)-8, epithelial neutrophil activating peptide (ENA)-78, vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-alpha) and antiinflammatory interleukin 1 receptor antagonist (IL-1RA) as biomarkers in EAA and IPF.
Seven IPF and eleven chronic EAA were enrolled to the study. Concentrations of IL-8, ENA-78, VEGF, TNF-alpha and IL-1RA in bronchoalveolar lavage fluid (BAL) supernatants were quantified using multiplex bead array assay. High resolution computed tomography (HRCT) alveolar and interstitial scores were assessed.
There was no difference in the levels of examined chemokines in BALF of IPF patients compared with EAA patients. The VEGF level in BALF of IPF group negatively correlated with the HRCT interstitial score (p<0.05), while the IL-8 BALF level positively correlated with the alveolar score (p<0.05) in the same group. No significant correlation between histological and cytokine score was found in the EAA group. There was no correlation between BALF TNF-alpha levels and HRCT scores in all examined groups. IL-1RA in BALF strongly correlated with HRCT alveolar score (p<0.001) in EAA group. There was no correlation between IL-1RA BALF values and either intestinal HRCT scores in EAA and IPF or alveolar HRCT score in EAA group.
We suggest that BALF concentrations of examined chemokines can not distinguish between chronic EAA and IPF. High IL-8 and low VEGF BALF concentrations might point toward more severe lung fibrosis in IPF. High IL-1RA concentrations may be the marker of initial stages of IPF.

PP166
The role of TGF-β1 signaling in alcohol-induced alveolar macrophage dysfunction
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Introduction: Alcohol (EtOH) addiction is a complex multifactorial disease that affect more than 70 million people and contributes to 1 in 25 deaths worldwide. Alcoholics have twice the incidence of intensive care unit (ICU)-related morbidity and mortality, commonly caused by acute respiratory distress syndrome (ARDS). Studies have shown chronic EtOH ingestion leads to increased oxidant stress and to the determinantal effects of EtOH on alveolar macrophage (MAC) maturation and function. Previous studies have shown chronic EtOH ingestion leads to increased oxidant stress (ROS), increased TGF-β1 production, increased fibronectin production, and decreased phagocytosis in AMs. However, the role of increased TGF-β1 signaling in EtOH-induced alterations of MAC has yet to be studied extensively.
Hypothesis: Our aim was to determine the role of TGF-β1, in EtOH-induced increases in MAC ROS production, induction of a pro-fibrotic phenotype, and decreases in MAC phagocytic function.
Methods: To test this hypothesis, NR8383 cells, a rat-derived MAC cell line, were treated with 0.08% EtOH, ± TGF-β1 neutralizing antibody for 5 days. Following treatment, the cells were analyzed for TGF-β1 production and secretion, MAC phagocytic function, ROS production, and the ability to induce fibroblast proliferation. Results: In NR8383 cells, treatment with EtOH resulted in increased production and secretion TGF-β1, decreased MAC phagocytic capacity, and increased fibroblast proliferation. Supplementation with TGF-β1 neutralizing antibody during treatment led to partial normalization of EtOH-induced increases in TGF-β1 production and secretion, ROS production, and fibroblast proliferation.

PP167
Differential inflammatory responses of nasal and bronchial epithelial cells to cigarette smoke extract
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Few studies compare the function of primary bronchial (PBEC) and nasal (PNEC) epithelial cells. Our aim was to compare the responses of paired PNEC and PBEC

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cultures to LPS stimulation and any modulatory effects of exposure to cigarette smoke extract (CSE). Cells, from subjects with COPD, were obtained by nasal or bronchial brushing and used at passage 3. They were stimulated for 24 h with LPS [0 – 25 μg/ml] ± pre-treatment with CSE. CSE was prepared by combining a 12 mg tar Marlboro cigarette through 25 ml of media. Supernatants were collected and IL-8 and IL-6 measured by ELISA. The localization of TLRL-4 was established by FACS. For the PNEC cultures, a brief incubation with CSE (4h) significantly inhibited LPS-induced IL-8 and IL-6 release (IL-8: 24h treatment with 25 μg/ml LPS alone 5457±424 pg/ml and with 4h CSE pre-treatment 3772±452 pg/ml). A more prolonged incubation with CSE (24h) was pro-inflammatory (IL-8: 25 μg/ml LPS alone 5485±562 pg/ml and with 24h CSE pre-treatment 7757±449 pg/ml). Although a brief incubation with CSE resulted in a lower percentage of surface and intracellular TLR4, a prolonged incubation was without effect. In contrast, both a brief and a prolonged exposure of PBEC cultures to CSE reduced LPS induced IL-8 release (IL-8: 24h treatment with 25 μg/ml LPS alone 5107±797 pg/ml, with 4h CSE pre-treatment 3345±60 μg/ml, and with 24h CSE pre-treatment 3010±328 pg/ml), and both lead to a reduced percentage of surface and intracellular TLRL4. There was minimal IL-6 release from the PBEC cultures. In conclusion, these data indicate that PNEC cultures are not a suitable surrogate for PBEC cultures in terms of their response to CSE/LPS combination treatment.

PP168 A three dimensional primary human lung tissue model provides the first evidence for Wnt11 as regulator of alveolar type II differentiation

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Adult stem cells are in the forefront of interest for lung tissue regeneration therapies. Progenitors that are vitally important for airway repair of alveolar type I (ATI) cells -the primary gas-exchange surface of the alveoli- are alveolar type II (ATII) cells that can flexibly turn into ATI and ATII cells on physiological demand. To develop targeted regeneration therapies, factors that can trigger such interchanges are needed to be identified. Studies, however, are hampered by the fact that recreation of the human adult airways microenvironment is difficult in vitro while ATI cells once removed from pulmonary tissues and placed into conventional cell culture systems lose their type characteristics and respond differently to stimuli.

Here we present an easily manipulable three dimensional (3D) primary human pulmonary micro-tissue model that maintains ATII phenotype of the alveolar epithelium. Also, we provide the first evidence that Wnt11 is one of the main regulators of ATII type differentiation which knowledge might enable targeted therapies in the future.

PP169 Bronchial lavage cell in radiation pneumonitis after radiotherapy for breast cancer

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Radiation pneumonitis is a complication of radiotherapy which limits its application in cancer therapy. AIm: To compare the bronchial lavage (BAL) findings in patients with symptomatic radiation pneumonitis (RP) versus asymptomatic RP.

Material and method: We evaluated 65 female patients with RP after radiotherapy for breast cancer. Results: Forty-nine patients were symptomatic (fever, cough and/or dyspnea) and 16 were asymptomatic. All patients had a newly discovered infiltrate or pleural effusion. Forty-nine patients were symptomatic (cancer symptoms - fever, cough and/or dyspnea) and 16 were asymptomatic. All patients had a newly discovered infiltrate or pleural effusion. The inflammation caused by radiation pneumonitis may lead to reactive hyperplasia of the bronchial epithelium, proliferation and increased expression of cytokines involved in inflammatory response.

We found that inflammatory markers were higher in symptomatic than asymptomatic patients. The most prominent inflammatory markers were IL-6, TNF-α, IL-8, and NOS2. The expression of these markers was significantly higher in symptomatic patients compared to asymptomatic patients.

Conclusion: Bronchial lavage analysis can be a useful tool in the diagnosis and monitoring of radiation pneumonitis after breast cancer radiotherapy.

PP170 Molecular interplay between inflammation and occurrence of proliferation: role of cadmium

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Introduction: Cadmium is one of the inflammation-related xenobiotics with potent carcinogenicity. The mechanism between inflammation and cell proliferation due to chronic cadmium exposure has not been studied yet (Lau AE, et al., Toxicol Appl Pharmacol 2006).

Objectives: The present study was undertaken to determine molecular mechanism of inflammation linked cell proliferation due to cadmium exposure in mice and lung cancer cell line.

Methods: Swiss albino mice and A549 cell line were chosen for experiments. Levels of different cytokines, expression level of cell cycle regulatory proteins estimated by ELISA, western blot and immunoprecipitation. Other techniques used scanning electron microscopy, histopathology and Cytotoxic assay. Cell cycle analysis, DNA fragmentation assay and RT-PCR experiments. Results: Prolonged exposure of low concentration of cadmium resulted in up regulation of proinflammatory cytokines and cell cycle regulatory molecules both in vivo and in vitro (Waalikes MP et al., Toxicol Sci 1999). We found that cadmium induced upregulation of epidermal growth factor receptor (EGFR) along with different proinflammatory cytokines. The major distinct feature of EGFR expression is promoting inflammatory responses along with cell proliferation.

Conclusions: These data provide a new insight into the relation between chronic inflammation and cell proliferation in vivo due to cadmium toxicity.

PP171 Alveolar macrophage-epithelial cell interaction during pulmonary inflammation

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We have shown that nanoparticle (NP) inhalation can trigger proinflammatory gene expression as lipocalin-2 (Lcn-2) in alveolar epithelial type II like cells (AEC) and osteopontin (Opn) in alveolar macrophages (AM). In vivo studies using AM or AEC failed to reproduce these responses. We hypothesize that macrophage-epithelial cell interaction is required to promote the inflammatory responses detected in vivo.

Murine cell lines representing AM (MHS), AEC (LA4), or cocultures of both cell types were incubated with carbon NP (CNP) or ZnO NP (positive control). LA4 cells were plated on cell culture inserts and upon their confluency, MHS cells were seeded on top. After 24 the apical medium was removed to create air-liquid interface conditions. After further 24h, suspensions of CNP (Printex90, 50 μg/ml) (10 μg) were added. Gene expression of inflammatory cytokines (Opn, Lcn-2, IL-6, CXCL1) and oxidative stress markers (HO-1, Me2) - was measured by qPCR after 6h incubation.

Regardless of condition, Lcn2 and Opn transcript levels were unchanged. CNP exposure caused 8fold increased IL-6 RNA levels only in MHS monolayers, no changes could be detected in LA4 co- or monolayers. IL-6 mRNA levels were, however, over 30fold higher in LA4 monolayers compared to MHS. ZnO exposure induced about 20fold increased transcript levels of HO-1 and Mt-2 in MHS/LA4 cocultures or LA4 and MHS monolayers, respectively.

CNP did not cause an oxidative stress response and unlike in vivo was not effective to trigger Opn and Lcn2 expression under any condition. Our results can not support the promotion of particle exposure triggered proinflammatory pathways by epithelial cell interaction. More complex culture conditions are necessary to reproduce proinflammatory responses at the in vitro level.

PP172 Microarray analysis reveals a novel link between WNT/β-catenin signaling and the fibrogenic immune response in idiopathic pulmonary fibrosis

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Rationale: Idiopathic pulmonary fibrosis (IPF) represents a fatal chronic lung disease with unresponsiveness to currently available therapies. Alveolar epithelial cell injury, enhanced extracellular matrix deposition and (myo)fibroblast activation are characteristics of IPF. Recent studies demonstrated a significant increase of (34.9±18.81% vs. 26.14±14.3%). Macrophages were decreased in all patients. Neutrophils were slightly increased (8.88% in symptomatic and 3.34% in asymptomatic) and eosinophils were normal in both groups (2.56% and 1.22%, respectively). CD8+ lymphocytes were increased in both groups with normal CD4/CD8 ratio (2.72 in symptomatic and 1.5 in asymptomatic group).

Conclusion: Cytokine expression in bronchoalveolar lavage fluid is a potential diagnostic tool for IPF. These data provide a new insight into the relation between chronic inflammation and cell proliferation in vivo due to cadmium toxicity.
WNTβ catenin signaling in IPF, driving in alveolar epithelial type II (ATII) cell proliferation and (myo)fibroblast activation. The downstream signaling mediators involved in the cellular effects of WNTβ catenin signaling remain elusive.

Methods and results: Here, we sought to identify signal molecules involved in WNTβ catenin function. We performed an unbiased whole genome microarray analysis from primary mouse ATI cells stimulated with WNT3A for different time points. From this microarray analysis we identified 224 and 223 genes to be significantly regulated by WNTβ catenin after 8h and 24h, respectively. Among these, the profibrotic cytokines interleukin (IL)-1β and IL-6 were identified and confirmed by quantitative qRT-PCR and ELISA. Both IL-1β and IL-6 were highly regulated on the mRNA and protein level in experimental and idiopathic human pulmonary fibrosis, as analysed by qRT-PCR and Western Blot analysis, and ELISA. Using WNT3A-treated transgenic TOPGAL mice, IL-1β and IL-6 induction by WNTβ catenin activation was confirmed in vivo.

Conclusion: Taken together, our microarray analysis of WNT3A-stimulated primary ATI cells revealed a novel link between the WNTβ catenin pathway and the fibrogenic immune response, which may foster the progression of fibrosis by affecting epithelial and immune cell function.

PP173
Role of mast cells and chymase in idiopathic pulmonary fibrosis
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Objective: The quantification of pulmonary MCs and CMCs revealed that their population was about 6 and 8 folds higher in IPF patients, as compared with donors. Also, MCs were separated as granulated and degranulated (activated) and index of granulation (IOG) (number of granulated/number of degranulated MCs) was evaluated.

Results: The quantification of pulmonary MCs and CMCs revealed that their population was about 6 and 8 folds higher in IPF patients, as compared with donors. There was a preponderance of perivascular MCs and CMCs in IPF lungs (p<0.05 versus donor lungs). Furthermore, we found that there was about 8 fold decrease of IOG in IPF patients as compared with donors. Finally, there was a strong accumulation of both MCs and CMCs in interstitial regions of the tissues (~65%) in comparison with other regions of the lungs.

Conclusions: The findings suggest that chymase released from activated MCs may be involved in the pathogenesis of IPF. Further investigations will unravel the underlying pathomechanism and substantiate chymase as a potential target for future therapeutic strategies.

PP174
Fibrosis as a consequence of immune dysregulation associated with HPA axis exhaustion: lessons from a 12-year experience in cystic fibrosis
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There are two principal mechanisms of inflammation control in the body. The first is realized by glucocorticoids (GCs) and catecholamines, the major stress hormones; the second is carried out by regulatory T cells (Treg). GCs stimulate a negative feedback mechanism, which protects the organism from products with negative feedback. Tregs maintain peripheral tolerance, realize a negative control of various immune responses and restrict inflammation. Normally, both mechanisms are well equalized. Such equilibrium may be disturbed due to multiple attacks of pathogens occurring in cystic fibrosis (CF) patients throughout life. The aim of the study was to reveal the signs of HPA axis depletion and regulatory T cell (Treg) accumulation in CF patients. Cohort of 83 CF patients without anti-inflammatory therapy and of 25 healthy children was enrolled into the study.

The results (see Table) show that along with low ACTH level, increased amounts of IL-10 and TGF-β1 may be revealed. Such immune abnormalities are associated with fibrosis including that in the liver. Ex vivo data confirm our assumption: long-term replacement therapy in the form of alternate course of prednisolone (0.2-0.5 mg/kg body weight every other day) significantly reduces cirrhosis frequency among 39 CF patients (p=0.001).

PP175
Telomerase activity profiles in lung cancer and idiopathic pulmonary fibrosis
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Introduction: Telomerase is a reverse transcriptase ribonucleoprotein (TERT) that synthesizes telomeric repeats using its RNA component (TERC) as a template to protect chromosome ends. There is a growing appreciation for the connection that exists between telomere maintenance deficiency states and conditions such as idiopathic pulmonary fibrosis (IPF) and various malignancies.

Aim: We aimed to evaluate telomerase expression levels (mRNA expression of both subunits TERT and TERC) in Bronchoalveolar Lavage Fluid (BALF) of patients with Lung Cancer and Idiopathic Pulmonary Fibrosis.

Patients and methods: We prospectively studied 21 BALF samples from patients with Lung Cancer, 22 BALF samples from patients with IPF and 12 BALF samples from control subjects. mRNA expression for hTERT and hTERC was measured by Real-Time RT-PCR.

Results: Human hTERC mRNA transcripts were detected in 2/21 (9.5%) cases of Lung Cancer, in 13/20 (65%) cases of IPF and in 4/12 (33.3%) of the controls subjects. BALF hTERC mRNA transcripts were significantly over-expressed in IPF as compared to Lung Cancer (2.06±1.51 vs 0.47±0.43, p=0.002) and a trend of increase remained when IPF was compared to controls (2.06±1.51 vs 0.07±0.05, p=0.055). No significant difference was detected in hTERC expression between controls and patients’ groups.

Conclusions: An increased expression of hTERC in IPF patients when compared to an attenuated hTERC expression in patients with Lung Cancer, suggests that telomerase may play significant, although different roles in fibrogenesis and carcinogenesis. These preliminary findings suggest the need for further investigation at the level of telomere length and telomerase activity.

PP176
Long-term anti-inflammatory treatment restores affected cytokine production in cystic fibrosis patients
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149 cystic fibrosis patients (mean age 12.4±6.0 years) were enrolled into the study. 74 patients were treated with basic therapy only and 75 individuals received besides the basic therapy anti-inflammatory treatment (AIT) with azithromycin (AZ, 500 mg orally three times a week; n=45), or prednisolone (PD, n=14) in the form of alternated course (0.3-0.5 mg/kg body weight every other day). 16 children received both AZ and PD. Duration of the AIT was 1 year or more. Plasma cytokine levels are presented in the Table.

The patients who received PD and AZ, combined therapy demonstrated the most pronounced changes in plasma cytokine levels. Their plasma TGF-β1 concentrations were comparable with those in healthy age-matched control (median value 17.7 pg/ml). Furthermore, in this group a significant elevation of pro-fibrotic IL-4 was associated with marked increase of anti-fibrotic IFNγ. The changes observed in AZ treated patients, in particular, increased IL-4 and TGF-β1 levels together with a tendency to fall of IFNγ are presumed to facilitate fibrosis and promote the potentially dangerous TH17 cell development.

PP177
cAMP-mediated regulation of fibroblast to myofibroblast differentiation in idiopathic lung fibrosis
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Rationale: Myofibroblasts are key effector cells in idiopathic pulmonary fibrosis (IPF). Their differentiation from fibroblasts is a major source of myofibroblasts. PGE2 inhibits myofibroblast differentiation. Its production is reduced in myofibroblasts due to depressed cyclooxygenase-2 (COX-2) gene expression. PGE2 inhibits
myofibroblast differentiation by increasing cAMP via EP2 and EP4 receptors. Our hypothesis is that exogenous PGE2 may trigger fibroblast differentiation through cAMP-mediated mechanisms.

Methods: Normal (F-NL) and fibrotic (F-F) primary human lung fibroblasts were treated with TGF-β to induce fibroblast to myofibroblast differentiation and PGE2, Forskolin (FSK) or Salmeterol (Sal) to reverse myofibroblast differentiation. To prevent myofibroblast differentiation, TGF-β and PGE2 were treated with PGE2 and TGF-β. COX-2, α-smooth muscle actin (αSMA), EP2 and EP4 were analysed by western blotting.

Results: F-F had increased uSMA and repressed COX-2 compared to F-NL. EP2/EP4 receptor expression does not differ between F-NL and F-F. F-F treated with PGE2 showed decreased α-SMA and increased COX-2. F-NL treated with TGF-β showed increased uSMA and reduced COX-2. F-NL treated with TGF-β and PGE2 had COX-2 and uSMA similar to control levels. F-F treated with Sal and FSK had decreased uSMA and increased COX-2.

Conclusions: Reduced PGE2 levels in F-F is not due to EP2 or EP4 receptor downregulation or PGE2 exerts myofibroblast differentiation and prevents TGF-β-induced myofibroblast differentiation in F-NL. FSK and Salme exert similar effects as PGE2. cAMP elevating agents inhibit myofibroblast differentiation and may offer an alternative therapeutic target.

PP178
Histological markers of epithelial-mesenchymal transition in idiopathic pulmonary fibrosis (IPF) provide evidence of an alternative repair process

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Introduction: Wound remodelling in the pathogenesis of idiopathic pulmonary fibrosis (IPF) has produced conflicting results from previous cell culture and animal model studies.

Aim: The aim of this study was to examine wound remodelling mechanisms in usual interstitial pneumonia (UIP), with emphasis on the role of epithelial mesenchymal transition (EMT).

Methods: Immunohistochemistry was used to assess cellular expressions of markers of EMT in paraffin embedded lung tissue samples from 21 patients with IPF, with comparisons made to histologically-defined normal lung sections from 19 control subjects.

Results: Hyperplastic type II pneumocytes in all UIP cases expressed the adhesion molecule E-cadherin with no expression of N-cadherin or TWIST. Expression of TWIST was restricted to fibroblasts/myofibroblasts. TGF-β1-induced myofibroblast differentiation and prevents TGF-β-induced myofibroblast differentiation in F-NL. FSK and Salme exert similar effects as PGE2. cAMP elevating agents inhibit myofibroblast differentiation and may offer an alternative therapeutic target.

Conclusions: Reduced PGE2 levels in F-F is not due to EP2 or EP4 receptor downregulation or PGE2 exerts myofibroblast differentiation and prevents TGF-β-induced myofibroblast differentiation in F-NL. FSK and Salme exert similar effects as PGE2. cAMP elevating agents inhibit myofibroblast differentiation and may offer an alternative therapeutic target.

PP179
Influence of leucocytes on Interleukin-8 in sputum and whole blood in cystic fibrosis

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Introduction: Sputum leukocytes but between blood leucocytes and IL-8 (r=0.528, p=0.007) in patients but not in controls. This might be explained by an increased apoptosis of airway leucocytes compared to blood leucocytes in CF (Tabary et al 2006).

Conclusion: IL-8 in the CF lung is regulated not only by LPS dependent mechanisms but are involved in innate and adaptive immune responses. Recent evidence suggests that viruses can cause mediator release from infected BECs with potential of activating dendritic cells (DCs). Therefore, we hypothesized that virally-infected BECs can induce DC activation.

Methods: Primary BECs monolayers were infected with rhinovirus (RV)-1 or

PP180
Does eradication of Helicobacter pylori decrease COPD exacerbation?

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Background: An epidemiological association between Helicobacter pylori (HP) infection and COPD patients was suggested in recent studies. HP IgG levels might be correlated with the severity of COPD. Chronic HP infection stimulates the expression of a variety of proinflammatory cytokines, such as IL-1, IL-8 and Tumor Necrosis Factor-α (TNF-α).

Objectives: to evaluate the effect of HP eradication on COPD exacerbations

Methods: 100 COPD HP seropositive patients were enrolled in the study, allocated into two (case/control) groups matched for age, sex, smoking habits, and COPD exacerbations in one year before the study. Baseline proinflammatory cytokine levels (PCL), including IL-1, IL-8, and TNF-α were measured. HP eradication was performed according to the current guidelines and the outcome was evaluated by assessing a change in the number of exacerbations in the case group compared to the control group.

Results: Two significant differences in the baseline PCL were observed in the two groups. COPD exacerbations were decreased after HP eradication in comparison with the placebo group (p=0.036). In the case group, a significant decrease in IL-1 (p=0.034), IL-8 (p=0.027), and TNF-α (p=0.037) was observed after eradication. At the end of study, IL-8 (p=0.013) and TNF-α (p=0.025) levels were significantly decreased, but IL-1 decrease was not significant (p=0.1). No significant changes in PCL were observed in the control group.

Conclusion: In this study HP eradication could decrease PCL and COPD exacerbations in HP seropositive COPD patients. This study supports the hypothesis that HP infection might play a proinflammatory role and co-trigger COPD with other factors.
UV-irradiated RV-1 for 8-48h. Real-time PCR was used to determine RV-1 infection of BECs. Mediator release by infected BECs was measured in supernatants by ELISA. Activation of monocyte-derived DCs following 24h incubation with UV-irradiated infected BECs supernatants was assessed by monitoring receptor expression by flow cytometry.

Results: Exposure of BECs to RV-1 resulted in a time-dependent increase in infection and cytopathic effect. RV-1 induced the release of IL-6, MCP-1, RANTES, MIP-3α, GM-CSF, IP-10, TNF-α and IL-8 in BECs. Culture of DCs with supernatants from RV-1-infected BECs induced CD86, HLA-DR and CD83 upregulation. RV-1-infected BECs and RV-1-activated DCs deficient in expression of DC to lyse control BECs supernatants caused CD86 upregulation. At a ratio where lyzed control cells had no effect, DC activation was still observed with UV-irradiated infected BEC supernatants.

Conclusion: Rhinovirus infection of epithelial cells causes release of pro-inflammatory mediators and DC maturation which may contribute to innate and adaptive immune responses.

PP184
Spectrum of anti-neutrophil cytoplasmic antibodies (ANCA) in patients with pulmonary tuberculosis overlaps with that of Wegener’s granulomatosis
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Introduction: Mycobacterial infections are known to induce the development of autoantibodies, some of which are also known to be diagnostic markers for some other diseases. This study was undertaken to determine the prevalence of autoantibodies like anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), anti-double stranded antibodies (anti-dsDNA) and anti-histone antibodies (AHA) in pulmonary Tuberculosis.

Materials & methods: Seventy pulmonary TB patients, 30 patients of interstitial lung disease (ILD) and 100 normals were studied. ANCA and AHA were detected by indirect immunofluorescence test (IIF). Anti-dsDNA and AHA were tested by ELISA.

Results: ANCA was detected in 30% cases, and of these 52.4% showed perinuclear pattern (p-ANCA), 38.1% cytoplasmic (c-ANCA) and 9.5% showed an “atypical” pattern. ANCA specificities by ELISA revealed that, 47.6% had anti-MPO, 19.1% had anti-Proteinase3 (anti-PR3) and 22% had anti-Lactoferrin (anti-LF) antibodies. ANA and AHA were present in 24.3% and 21.3% cases respectively whereas anti-dsDNA antibodies were absent.

Conclusion: The presence of autoantibodies in TB patients could have a multifactorial etiology. Clinically relevant is the presence of anti-PR3 antibodies. This finding along with pulmonary and renal manifestations could lead to a false diagnosis of Wegener’s granulomatosis or vice versa because these autoantibodies may be present in both diseases.

PP185
Increased phospholipases A2 activity in alveolar macrophages at low oxygen and influence of bacterial lipopolysaccharides
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Acute respiratory distress syndrome (ARDS) is a lung injury of high mortality rate and sepsis is one of the most frequent cause of ARDS. Alterations of pulmonary surfactant, in which dipalmitylophosphatidylcholine (DPPC) is a major component, is an early pathophysiological event in ARDS. In sepsis-induced acute lung injury, edema and atelectasis may result in low ventilation and reduced O2-tension around alveolar macrophages (AM). Therefore, we examined the effects of bacterial lipopolysaccharides (LPS) and low oxygen on enzymatic hydrolysis of DPPC in AM. AM were cultured for 20 h with 1, 10, 50 μg/ml LPS. We found a significant increase in hydrolysis of DPPC by phospholipases inside AM and in culture medium in dose- and time-dependent manner. The activity was maximal after 20 h of incubation with 50 μg/ml LPS and was 41% and 118% (p < 0.01) above controls for intra- and extracellular DPPC hydrolysis correspondingly. AM were exposed for 20 h to the normal (21%) and the low (17, 13, 10, 5%) oxygen. A progressive reduction in the concentration of O2 resulted in enhanced phospholipase activity to 19% (p ≤ 0.05). Secretory enzymatic activity was less sensitive, it only increased O2-tension around alveolar macrophages. We investigated whether AR inhibition could prevent ovalbumin (OVA)- and ragweed pollen extract (RWE)-induced airway inflammation in mice model of asthma.

Mice Sensitization by an Intraperitoneal injection of RWE/OVA in adjuvant Al(OH)3 twice on days 0 and 4 for RWE and one week apart for OVA. Challenge intranasally (RWE) or by nebulization (OVA). Airway inflammation confirmed by BAL cytology, Eosinophils infiltration in lung, Cytokines and chemokines levels. Phenotype characterization and production of inflammatory cytokines, accumulation of eosinophils in airways and sub-epithelial regions, macin production in the bronchoalveolar lavage fluid, and airway hypersensitivity, elevated IgE level and release of Th2 cytokines in the airway and treatment with AR inhibitors markedly reduced these pathological changes in mice. In SAEC, treatment with TNF-alpha, LPS- or RWE-induced apoptosis, reactive oxygen species generation, the release of inflammatory markers IL-6, IL-8, and PGE2 and activation of NF-kappaB and AP-1. Our results indicate that AR inhibition could be a novel therapeutic approach for preventing airway inflammation such as allergic asthma.

W1
II/IL1RA axis mediates bone marrow cell senescence and eosupressus
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Introduction: Stem cell senescence may be involved in the pathogenesis of chronic obstructive pulmonary disease (COPD). Interleukin-1 receptor antagonist (IL1RA) is a naturally occurring inhibitor of IL1. Ortiz et al. (2007) showed that intravenous stem cell (MSC)-mediated lung repair is also regulated by IL1RA after bleomycin-induced lung injury.

Aims and Objectives: The study was conducted to determine the effect of IL1RA-converting enzyme and IL1RA overexpression protected the lungs from aging-associated pathology compared to the background strain. CTX assays showed that IL1RA+ mice had reduced MSCs compared to the IL1RA TG mice (4.6 ± 1.0, p = 0.001). The study was conducted to determine the effect of IL1RA on aging-associated pathology compared to the background strain. CTX assays showed that IL1RA+ mice had reduced MSCs compared to the IL1RA TG mice (4.6 ± 1.0, p = 0.001).

Results: Hoe staining of fixed tissue showed that IL1RA+ mice had reduced MSCs compared to the background strain. The absence of IL1RA-converting enzyme and IL1RA overexpression protected the lungs from aging-associated pathology compared to the background strain. CTX assays showed that IL1RA+ mice had reduced MSCs compared to the IL1RA TG mice (4.6 ± 1.0, p = 0.001). The study was conducted to determine the effect of IL1RA on aging-associated pathology compared to the background strain. CTX assays showed that IL1RA+ mice had reduced MSCs compared to the IL1RA TG mice (4.6 ± 1.0, p = 0.001).
W3
Allergic airway responses to aeroallergens are differentially regulated by IL-13 receptor alpha 1 and dependent on IL-13:IL-4 ratios
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Background: Studies using IL-33/IL-13 mice demonstrated a critical role for IL-13 receptors in all allergic-induced airway responses except eosinophilia. However, previous experiments were limited to mice sensitized with intraperitoneal OVA and alum.

Aims: To define the role of IL-13Rα1 in allergic-airway inflammation in response to aeroallergens and mucosal sensitization.

Methods: Wild type and IL-33/IL-13 mice were challenged with Aspergillus fumigatus (Asp) or house dust mite (HDM) extracts (10 mg/mouse, 9 intranasal challenges). Alternatively, Asp was absorbed to alum (100 mg + 1 mg), mice were sensitized (days 0 and 14, intraperitoneal) and challenged (days 24 and 27, intranasal). BALF was assessed for differential cell counts (Diff-Quick), TH2 cytokine and chemokine levels by ELISA, Lung histology and resistance were assessed by H&E, PAS stain and flexiVent respectively.

Results: Asp- and HDM-induced AHR and mucus production was IL-13Rα1-dependent. Eosinophil recruitment to the lung as well as CCL17, CCL22 and IL-5 production were IL-13Ra1 dependent following Asp-challenge but IL-dependent. Eosinophil recruitment to the lung as well as CCL17, CCL22 and IL-5 production were IL-13Ra1 dependent following Asp-challenge but IL-dependent.

Conclusions: We highlight IL-13Rα1 as a key regulator of allergic lung responses following aeroallergen sensitization and challenge. Nevertheless, outcomes of IL-13Rα1-targeted asthma therapy may vary according to allergen-induced IL-4:IL-13 ratios.

W4
Transcription factors GATA-3 and T-bet as crucial markers of allergic bronchial asthma
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Aim: The aim of the study is to establish the features of expression of GATA-3 and T-bet in bronchial asthma (BA).

Methods: 20 healthy controls, 44 patients with allergic and 42 with non-allergic BA were examined. GATA-3 and T-bet expression in peripheral lymphocytes were analyzed by Western blotting after the cells were lysed. Western blotting was performed through the standard procedure. Antibodies against GATA-3 (Abcam, UK) and T-bet (Santa Cruz Biotechnology, UK) were used. The level of protein analyzed according to p-tubulin using anti-tubulin antibody (Sigma Aldrich, USA).

Results: The expression of GATA-3 was significantly increased and expression of T-bet was significantly decreased in lymphocytes of patients with allergic BA compared to healthy (p=0.04) and non-allergic BA groups (p=0.005). The level of GATA-3 and IL-4 receptor positively correlated with the degree of airflow obstruction (r=0.4, p=0.011; n=41) and positively correlated with the intensity of steroid therapy (r=0.33; p=0.033; n=42). The level of T-bet in non-allergic BA positively correlated with the prevalence of asthmatic triad (r=0.4, p=0.011; n=41) and the drug intolerance (r=0.43; p=0.005; n=42).

Conclusion: GATA-3 and T-bet may play a key role in the pathophysiology of BA. The expression of GATA-3 and T-bet may serve as a markers of allergic BA to provide necessary dose of steroids in patients with BA. This study suggests that allergic BA underlie the high level of TH2-cytokines production in allergic disease. The work was supported by Saint-Petersburg government grant 28-04/17 (Certif. PSP00591) and by Saint Petersburg State Medical University grant named after Pavlov “Research grant of the year” for the best scientific work.

W5
Chemokine and relative receptors mRNA levels in blood of COPD patients
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Chronic obstructive pulmonary disease (COPD) is respiratory system pathology with remitting course and progression of respiratory dysfunction. Chemokines and their receptors is a cutting edge of chronic inflammation development during COPD. Chemokines and chemokine receptors mRNA expression in whole blood is pivotal reflection in COPD clinical overview. In our study we tried to examine chemokine-receptor balance in COPD progressions. The whole blood samples of 20 patients with COPD were investigated concerning mRNA encoding cytokin, eotaxin-2, MIP-1alpha, MIP-1beta, IL-8, RANTES, CCR1, CCR3, CCR5, CXCR1, and CXCR2. As a control group blood of 23 healthy volunteers was studied. The total RNA was extracted accordingly manufacturing procedure, followed by reverse transcription, gene-specific PCR and semi-quantitative analysis were performed using beta-actin as a reference gene. All patients were male (mean age 58.5±7.2) and had a long smoking history. The age of volunteers was 53.3±6.4 and they had no smoking history. The results of analysis for chemokines and receptors were analyzed according to clinical features of COPD. The statistically significant increasing of IL-8 and MIP-beta mRNA in COPD patients was established relatively to control, meanwhile gene expression of MIP-1alpha CCR1, CCR3, CCR5, CXCR1, and CXCR2 was decreased in COPD patients. Eotaxin mRNA level in blood directly correlates with exacerbation in COPD patients (r=0.88, p=0.004). Patients with 2nd stage of respiratory failure have lower CCR1 (p=0.019) mRNA expression in comparison of 1st stage. The level of pulmonary hypertension is directly correlates with eotaxin-2 mRNA expression (r=0.52, p=0.01).

W6
Ascorbate and deferoxamine administration post chloride exposure decrease mortality and lung injury in mice
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Chlorine (Cl2) gas exposure poses an environmental and occupational hazard that frequently results in acute lung injury. There is no effective treatment. We assessed the efficacy of antioxidants in decreasing mortality and lung injury as a result of Cl2 toxicity to mice exposed to 600 ppm of Cl2 for 45 minutes and returned to room air. Ascorbate and deferoxamine were administered intramuscularly every 12 hours (h) and by nose-only inhalation every 24 h for 3 days starting after 1 h post-exposure. Control mice were exposed to Cl2 and treated with vehicle (saline). Mortality was reduced four-fold in the treatment group compared to the control group (22% versus 78%; p<0.007). Surviving animals in the treatment group had significantly lower protein concentrations, cell counts and epithelial cells in the bronchoalveolar lavage (BAL). Elevated ascorbate levels in the lung tissue correlated inversely with protein levels as well as with number of neutrophils and epithelial cells in the BAL. In addition lipid peroxidation was reduced 3-fold in the BAL of mice treated with ascorbate and deferoxamine when compared to the control group. Administration of ascorbate and deferoxamine reduces mortality and ameliorates lung injury through reduction of alveolar-capillary permeability, inflammation, and epithelial shedding and lipid peroxidation.

W7
Comparison of ribavirin and oseltamivir in treating A/Caifornia/04/2009 (H1N1) influenza virus in mice
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Increasing cases of oseltamir resistant H1N1 (2009) viruses are being reported. Ribavirin is an antiviral agent effective against hepatitis C and respiratory syncytial virus. Our objective was to compare the efficacy of ribavirin and oseltamir in treating mice infected with mouse adapted A/Caifornia/04/2009 influenza virus in terms of mortality and lung injury. 48 female BALB/c mice were used in the study and randomized to 3 groups: 1) A/Caifornia/04/2009 & Ribavirin, 2) A/Caifornia/04/2009 & Oseltamir, 3) A/Caifornia/04/2009 & Placebo. Mice were challenged intranasally with mouse adapted A/Caifornia/04/2009 influenza virus and treatments started 5 hours pre-infection and subsequent treatments were administered at 12:1 hours apart for 5 days. At days 3 and 6 post-infection 3 mice from each group were euthanized for broncho-alveolar lavage analysis and lung viral loads determination. We also assessed I4-day survival, protein levels, total cell counts and chemokine and cytokine profiles in the BAL. etc.

Ribavirin and oseltamir groups had significant increase in survival and significant decrease in lung viral loads and protein levels in BAL compared to untreated group. Ribavirin group insignificantly higher neutrophil counts on Day 3 compared to oseltamir and untreated groups. Both groups had significantly lower levels of KC, RANTES, MIP-1a and MIP-1b at day 3 compared to untreated ones. Ribavirin group had minimal production of IL-6 and IFN-γ and IL-10 at days 3 and 6 while oseltamir group had increased levels of IL-6, IL-12, and IFN-γ at day 6. Our results indicate that ribavirin is equally effective with oseltamir in improving survival and mitigating lung injury caused by H1N1 influenza virus infection.
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Nitrogen dioxide

Nitric oxide: synthase and nitric oxide inhibitors

Noninvasive ventilation

Nodules

Nitric oxide: synthesis and nitric oxide inhibitors

Nitrogen dioxide

Nitrite

Nitrates
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Pleural diseases
Pleural effusion
Polyomaviruses
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Pleural neoplasms
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